Depression & Metabolic Syndrome

Vogelzangs, N.

2010

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Nicole Vogelzangs

This thesis was prepared within the EMGO Institute for Health and Care Research (EMGO$^+$). EMGO$^+$ participates in the Netherlands School of Primary Care Research (CaRe) which was re-acknowledged in 2005 by the Royal Netherlands Academy of Arts and Sciences (KNAW).

Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

Further financial support for the publication of this thesis was kindly provided by:
Department of Psychiatry, VU University Medical Center, Amsterdam
EMGO$^+$, VU University Medical Center, Amsterdam
Lundbeck B.V., Amsterdam
Mediq Direct Diabetes, Didam
Servier Nederland Farma B.V., Leiden
Vrije Universiteit, Amsterdam

Printed by Ipskamp drukkers, Enschede, the Netherlands

ISBN: 978 90 8659 447 4

VRIJE UNIVERSITEIT

Depression & Metabolic Syndrome

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op vrijdag 23 april 2010 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Nicole Vogelzangs

geboren te Arcen en Velden

promotoren: prof.dr. B.W.J.H. Penninx
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Contents

Chapter 1

General introduction

Parts of this chapter were taken from:

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Aging and behavioral medicine
In: Steptoe A et al. Handbook of Behavioral Medicine
In press

Almost a century ago, in 1921, Ernst Kretschmer concluded in his publication 'Körperbau und Charakter' (Physique and Character),[1] based on systematic observations, that depressive symptoms are more common among persons with a pyknic body build. He described the pyknic type as

> *"… characterized by the pronounced peripheral development of the body cavities (head, breast, and stomach), and a tendency to a distribution of fat around the trunk, with a more graceful construction of the motor apparatus (shoulders and extremities)".*

Although the term pyknic build did not survive, the description he gave of this specific body build does closely resemble that of later observations. In 1956, Jean Vague wrote:[2]

> *"Android obesity, with upper body predominance and pronounced muscle-blood development, leads to metabolic disturbances. It not only is associated with premature atherosclerosis and diabetes, but it is also the usual cause of diabetes in the adult in 80 to 90 per cent of cases. … Overactivity of the pituitary-adrenal axis appears to be the most probable cause both of android obesity and it complications."*

With this description Vague paved the way for what we now call the 'metabolic syndrome', a clustering of cardiovascular risk factors including abdominal obesity, unfavorable lipid profile, hypertension and hyperglycemia. Recent studies have abundantly confirmed that abdominal obesity and the metabolic syndrome are associated with increased risks of diabetes, atherosclerosis, and cardiovascular disease.[3-9]

These early perceptions are not only in agreement with the concept of the metabolic syndrome, but Kretschmer's observations also indicate that the metabolic syndrome might be associated with depressive disorders and symptoms. Indeed, some recent studies have linked depressive symptoms to individual components of the metabolic syndrome, e.g. hypertension, obesity, or high blood glucose levels.[10-12] Considering that both depression and cardiovascular disease might be linked to metabolic disturbances, it has been hypothesized that the metabolic syndrome could play an important mediating role in the frequently described association between depression and cardiovascular disease.[13-15] Gaining more explicit knowledge on the association between depression and the metabolic syndrome could enhance insight into depression and cardiovascular disease comorbidity. However, until recently, only very few studies have investigated whether depressive disorders or symptoms are associated with the total metabolic syndrome package or have compared the relative influence of individual components. Besides, the temporal direction of the associations between depression and metabolic abnormalities remains unclear. Also, what exactly then causes these metabolic disturbances and their consequences? A hint for this was already given by Vague: hyperactivity of the hypothalamic-pituitary-adrenal (HPA)-axis, which indeed in the past decades has recurrently been linked with depressive disorders[16,17] and some cardiovascular risk factors.[18,19] Integrating the above presented, this thesis will focus on the reciprocal associations between depression and the metabolic syndrome in older persons, taking herein into account a possible role for the HPA-axis.

Focus is given to older populations as both depressive symptoms and cardiovascular conditions are highly prevalent among the aged.[20,21] In the current chapter, background information on issues relevant for this thesis will be given, finishing with a thesis outline.

Aging

In the Western world, the old and especially the oldest of the old comprise the fastest growing segment of our population. This is due to a decreasing trend in the number of children born as well as to dramatic changes in mortality leading to increased life expectancy. In the Netherlands, 14% of the population in 2007 was 65 years or older, of whom 25% was 80 years or older. It is expected that in 2050 even 24% of the Dutch population will be 65 years or older.[21] Of this 65-plus population, 57% are women and, as life expectancy has consistently been higher for women than for men, this percentage is increasingly higher in older age groups.[21] Consequently, in absolute terms aging is affecting women more than men.

Aging has a profound impact on the individual. For the most part, individual aging is associated with many adverse changes in human anatomy and physiology. For a large part of adult life, people are normally provided with 'biological' reserves. In later life, these reserves are reduced, which can cause weakening of one or another biological function essential to life. As a result, conditions such as heart disease, cancer, respiratory infection, or osteoarthritis may arise. The biological age-related changes and the consequent development of degenerative and chronic conditions, have a large impact on the physical functioning and behaviors of older persons. The most important cause of morbidity and mortality at older age is cardiovascular disease.[21]

Depression, depressive symptoms and other psychosocial factors

In the Netherlands, yearly about 6% of the adult population suffers from a depressive disorder,[21] which is comparable to other countries across the world.[22] Although the prevalence of depressive disorders is rather stable over years, the relative impact of depressive disorders on public health is enormous and increasing. According to the World Health Organization depression ranks high in the top ten of diseases causing great worldwide burden of disease and it is projected that in 2030 depression will be leading the disease burden list.[23] High disease burden of depression is particularly caused by a marked decline of quality of life. A diagnosis of major depressive disorder includes a depressed mood and/or a noticeable decreased interest or pleasure of almost all activities most of the day, nearly every day, for a minimum of two weeks.[24] These key symptoms are accompanied by fatigue or loss of energy, marked changes in appetite or weight, sleep disturbances, psychomotor agitation or retardation, feelings of worthlessness or excessive guilt, diminished ability to concentrate or indecisiveness, and/or recurrent thoughts of death or suicidal ideation. In total, a person experiences at least five of the above described symptoms and is clearly impaired in every day functioning.

Also in old age, the most common psychological problems experienced are depressive symptoms. Prevalence rates of depressive problems in later life vary considerably depending on the sample studied and methods used. Studies in clinical settings generally find much

higher prevalences than studies in community settings, and studies applying psychiatric diagnostic criteria for depressive disorders find much lower prevalences than studies using symptom checklists. It is possible to score relatively high on a symptom checklist without meeting diagnostic criteria for depressive disorders. Specifically in older populations, symptom checklists identify for a large part persons who do not fulfill the diagnostic severity threshold of psychiatric depressive disorders. This condition is often referred to as 'subthreshold depression'. As confirmed in several aging studies, major depressive disorder affects about 2-4% of the community-dwelling population.[25] Contrary to what some people might expect, psychiatrically defined depression appears to be less prevalent among older adults than among young and middle-aged adults, although the presence of depressive symptoms is much more common.

Table 1 shows the 1-year prevalence rates of depressive disorders among participants of the community-based Longitudinal Aging Study Amsterdam (LASA) (see also[26]). These results confirm a prevalence of 1-4% for major depressive disorder in old age, and much higher prevalence rates of subthreshold depressive symptoms (8-21%). Also, whereas the prevalence of depression does not clearly increase over time, the rates of subthreshold symptoms do. It is important to realize that a large proportion of older persons with a depressive disorder have had prior episodes during earlier phases of their lives. As in younger age groups, older women generally show higher rates of depressive disorders and symptoms than older men.

Table 1. Presence of depressive and anxiety symptoms and disorders in older men and women in different age groups in LASA

	Men			***Women***		
Age group (in years)	55-65	65-75	75-85	55-65	65-75	75-85
N	*490*	456	560	526	517	558
Depression						
Major depressive disorder [a]	1.2%	1.1%	0.5%	3.4%	3.5%	2.0%
Subthreshold depression [b]	8.2%	8.1%	13.2%	9.7%	14.1%	21.0%
Anxiety						
Panic disorder [a]	0.4%	0.2%	0.2%	1.5%	1.5%	0.4%
Social phobia [a]	1.2%	0.4%	1.1%	2.1%	1.5%	1.8%
Generalized anxiety disorder [a]	1.8%	2.0%	2.1%	4.6%	5.2%	4.1%
Subthreshold anxiety [c]	5.3%	4.2%	4.5%	6.7%	7.7%	7.2%

[a] 1-Year prevalence rates based on diagnostic DSM III-criteria using the Diagnostic Interview Schedule. [b] Indicated by Center for Epidemiologic Studies Depression Scale ≥ 16, but no major depression diagnosis. [c] Indicated by Hospital Anxiety and Depression Scale - Anxiety subscale ≥ 8, but no anxiety disorder diagnosis.

Next to depression, anxiety symptoms are also relatively common in old age. Table 1 additionally shows 1-year prevalence rates of the main anxiety disorders (panic disorder, social phobia and generalized anxiety disorder) and subthreshold anxiety symptoms in LASA (see also[27]). Other psychosocial factors are important in aged persons as well, for instance life events such as the loss by death of age-peers such as siblings and friends, but also of one's own partner. Widowhood has systematically been shown to increase the risk of developing consequent depression and anxiety disorders,[28] which might be especially true for men.[29] Increasing age also brings changes in relationship needs, for example as the result of increasing impairment. In general, when adjustment to the burdening circumstances related to aging is inadequate, an older person might experience substantial psychological stress and consequent symptoms of depression or anxiety (e.g.[30]). In the present thesis the main focus will be on depression, but some additional attention will be given to other psychosocial factors (anxiety, recent life events, emotional support).

Depression and cardiovascular disease

Heart disease, just like depression, is on the top list of diseases with the greatest loss of 'disability adjusted life years'. The World Health Organization projected that in 2030 depression and heart disease will take in the first and second place, respectively, in high-income countries and second and third worldwide.[23] The public health impact of depression and heart disease is especially high, considering that an abundant amount of literature has associated depression with cardiovascular disease, linking depression with poorer cardiovascular outcome, relating depression with increased risks of cardiovascular events or mortality, and showing an increased onset of depression after cardiovascular events. Meta-analyses on studies in heart patients and in the general population suggest that depression is associated with a twofold increased risk of cardiovascular events and mortality.[31-36] Although these systematic reviews do not explicitly distinguish between studies using middle-aged and older populations, it is good to realize that in fact the majority of these studies have been conducted among older persons, simply because morbidity and mortality most commonly occur in the oldest age groups. Several hypotheses exist to explain the high comorbidity between depression and cardiovascular disease, one of which suggests the metabolic syndrome as a linking mechanism.[13-15]

Metabolic syndrome

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin - metabolic risk factors - that places persons at risk for developing (atherosclerotic) cardiovascular disease and type 2 diabetes mellitus and was first described by Reaven in 1988 as Syndrome X.[38] The metabolic risk factors that come together in the metabolic syndrome include (abdominal) obesity, dyslipidemia, hypertension and hyperglycemia. Although these factors often cluster and therefore can be seen as a syndrome, there is still debate on whether there is one underlying cause of the metabolic syndrome.[39] Insulin resistance and abdominal obesity are regarded as the key candidates for explaining the grouping of metabolic risk factors. Regardless of the cause, the metabolic syndrome identifies individuals at an elevated risk for cardiovascular disease and diabetes.[3-9]

Different definitions of the metabolic syndrome exist, but most widely used are the US National Cholesterol Education Program - Adult Treatment Panel III (ATP III) criteria.[40] The ATP III guidelines define metabolic syndrome as the presence of three or more of the following criteria:

1. ***Abdominal obesity***: waist circumference > 102 cm (men) or > 88 cm (women);
2. ***Hypertriglyceridemia***: triglyceride levels ≥ 150 mg/dl (1.7 mmol/l);
3. ***Low high-density lipoprotein (HDL) cholesterol***: HDL levels < 40 mg/dl (1.03 mmol/l; men) or < 50 mg/dl (1.30 mmol/l; women);
4. ***Hypertension***: blood pressure ≥ 130/85 mmHg or use of antihypertensives;
5. ***Hyperglycemia***: fasting blood glucose ≥ 110 mg/dl (6.1 mmol/l) or use of anti-diabetic medication.

The metabolic syndrome is very common; the prevalence among US adults is estimated to increase from 6.7% among persons aged 20-29 years to 43.5% for persons aged 60 years and over.[41] In the Netherlands the prevalence of the metabolic syndrome is similar or perhaps somewhat lower: results from LASA show a prevalence of the metabolic syndrome of 36.5% among persons aged 65 years and older.[42] Several studies have associated individual metabolic disturbances with depressive symptoms.[10-12]

Hypothalamic-pituitary-adrenal axis

During acute physical or psychological stress the hypothalamic-pituitary-adrenal (HPA)-axis becomes activated. Under control of the hypothalamus, corticotrophin releasing hormone (CRH) is released and stimulates the pituitary to circulate adrenocorticotrophic hormone (ACTH), which in turn signals to the adrenal cortex to release cortisol. Direct effects of cortisol are amongst others mobilization of glucose and free fatty acids, a decrease of growth and sex hormones levels, an increase in cardiac output and blood pressure, and tempering of the activated immune system.[14,43-45] The purpose of this acute stress reaction is to help the body regain homeostasis. Although usually very functional, chronically elevated cortisol, for instance due to chronic stress, can cause tissue damage and neuroendocrine dysregulation. Chronic hyperactivity of the HPA-axis has recurrently been noted in at least a subgroup of depressed persons.[16,17] Furthermore, high levels of cortisol have been associated with specific cardiovascular risk factors and accelerated atherosclerosis.[18,19] These unwanted effects of hypercortisolemia are most pronouncedly seen in persons with Cushing's syndrome, in which prolonged excessive cortisol secretion causes amongst others abdominal obesity and depressive symptoms. Considering the above, it was Björntorp who first explicitly hypothesized that chronic stress and/or depression results in abdominal obesity and associated comorbidities such as cardiovascular disease, through long-term activation of the HPA-axis.[14] Considering a possible role of the HPA-axis in the association between depression and metabolic syndrome is therefore very desirable.

Epidemiological research

Literally 'epidemiology' means the study of epidemics. Contrary to what many people might think, epidemiology is not restricted to the study of infectious diseases. An epidemic in this context has to be interpreted as a disease or other health-related condition which is more prevalent in one population defined by either time, place or a multitude of other possible characteristics (e.g. demographics, social factors, other diseases, environmental factors, treatment) than in another population which importantly differs on these characterizations. The task of the epidemiologist is not only to describe prevalences and incidences of disease in specific populations, but also to examine which factors influence the presence or occurrence of disease or health-related conditions. By systematically comparing persons that vary on well-described characteristics, it is possible to gain important knowledge about indicators, causes, and consequences of disease, which might ultimately help in prevention and treatment of the conditions studied. One important tool of the epidemiologist, which will be applied in this thesis, is the prospective observational cohort study. In this type of study a random sample of a specified population undergoes a baseline assessment in which a large number of features of the individuals of this sample are inventoried. This can be done by means of questionnaires, interviews, taking blood samples, medical assessments, and so on. During subsequent years, for as long as is practically and ethically possible, these same persons are followed-up and re-assessments of important characteristics and outcomes will take place at pre-specified moments (e.g. every one or two year). Major advantages of this type of study are the prospective nature and the ability it brings to study the natural course of disease.

Studies used in this thesis

Several large prospective cohort studies form the basis of the present thesis. The *Health, Aging and Body Composition (Health ABC) study* is a prospective population-based cohort study among 3075 well-functioning white and black older persons, aged 70-79 years, from Memphis, Tennessee and Pittsburgh, Pennsylvania (US). The primary goal of this study is to identify determinants and consequences of body composition changes during the aging process. Both baseline and 5-year follow-up data were used in this thesis. Another study that provided data was the *Invecchiare nel CHIANTI (aging in the Chianti area; InCHIANTI) study*. This study was conducted among 1155 community-dwelling older persons, aged 65 years and older, living in the Chianti area, Italy, originally initiated to examine the influence of multiple physiological subsystems on the ability to walk. Data from the baseline measurement and 3 and 6 years follow-up were available. Also, the *Longitudinal Aging Study Amsterdam (LASA)* included an population-based sample of older persons. LASA focuses on the interrelationships between and changes in physical, emotional, cognitive and social functioning during aging. From three regions in the Netherlands (Amsterdam, Zwolle, Oss) 3107 participants, aged 55-85 years, underwent the baseline assessment in 1992/1993. In the present thesis data from the first follow-up measurement in 1995/1996 were used. Lastly, the *Netherlands Study of Depression and Anxiety (NESDA)* is a prospective cohort study among 2981 persons, aged 18-65 years, with a current or remitted depressive or anxiety disorder diagnosis and diagnosis-free controls. Main objective of

NESDA is to describe and examine predictors of the long-term cause and consequences of depressive and anxiety disorders, while integrating biological and psychosocial research paradigms. Baseline data of the NESDA study were available for the present thesis.

General aim

Bringing together the observations presented in this General Introduction, a schematic presentation of the research model for the present thesis is shown in Figure 1. This model suggests that depression might increase the risk of cardiovascular disease by first advancing the occurrence of metabolic syndrome. Hyperactivity of the HPA-axis in depressed persons might be an important underlying mechanism through which the risks of metabolic syndrome and subsequent cardiovascular disease are increased. Concurrently, the metabolic syndrome, as precursor of cardiovascular disease, is theorized to raise the occurrence of depression. Possibly, HPA-axis disturbances play a role in this pathway as well. Both pathways might provide an explanation of the frequently reported co-occurrence of depression and cardiovascular disease.

Therefore, the general aim of this thesis is to examine whether depressive disorders or symptoms are associated with, predict, or follow metabolic disturbances, such as present in the metabolic syndrome and obesity. In addition, this thesis investigates whether the HPA-axis, as indicated by serum and urinary cortisol levels, plays a mediating role between depression on the one hand and metabolic syndrome and cardiovascular disease on the other hand. Knowledge to be gained by this thesis could increase our understanding of pathophysiological processes linking mental and physical health, which might be very useful for prevention and treatment of both depression and cardiovascular disease. To study these research questions an epidemiological approach is taken.

Outline of this thesis

This thesis will first examine whether depression and metabolic syndrome are cross-sectionally associated, followed by the exploration of a mediating role in this association for the HPA-axis. Subsequently, longitudinal examinations will investigate the temporal direction between depression and metabolic syndrome, with a special focus on (abdominal) obesity. Lastly, the presumed role of cardiovascular disease in the thesis model is tested by examining its association with depression and cortisol. Throughout the thesis the relative importance of individual metabolic disturbances in their association with depression will be compared.

The numbers in Figure 1 refer to the thesis chapters which focus on the corresponding research questions. **Chapter 2** uses data from the Health ABC study to examine the cross-sectional association between several psychosocial risk factors (depressive and anxiety symptoms, recent life events, and inadequate emotional support) and metabolic syndrome in older persons. Using data from the InCHIANTI study, **Chapter 3** investigates the associations between late-life depressive symptoms and urinary cortisol with metabolic syndrome and it components. Specifically, the role of urinary cortisol in the association between depressive symptoms and metabolic syndrome is explored. In **Chapter 4** the relationships between late-life depressive symptoms and serum cortisol with metabolic

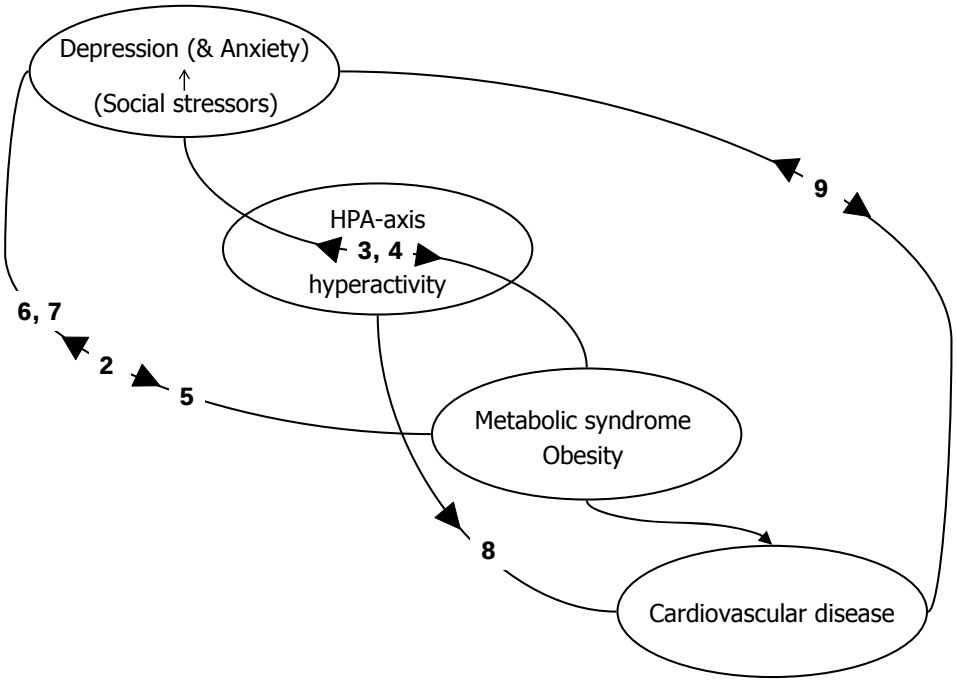

Figure 1. Research model of this thesis.
Numbers indicate thesis chapters.

syndrome (components) are extended in LASA to include major depressive disorder diagnoses. Leaving the cross-sectional examinations, the next two chapters focus on (abdominal) obesity, as possibly the most important component of metabolic syndrome, and longitudinally examine whether depressive symptoms might bring about changes in (abdominal) obesity (**Chapter 5**) or whether (abdominal) obesity could predict the onset of depressive symptoms in depression-free older persons (**Chapter 6**). These two chapters make use of the Health ABC study dataset. **Chapter 7** describes both the onset and persistence of depressive symptoms over 6 years of follow-up in older persons with and without metabolic syndrome at baseline by means of the InCHIANTI data. In **Chapter 8**, also based on the InCHIANTI study, the question is asked whether the often assumed association between high cortisol levels and increased risk of cardiovascular disease indeed exists. The last scientific chapter (**Chapter 9**) leaves the older population and examines whether the frequently described association between depression and cardiovascular disease, a basic fundament of this thesis, also exists within a younger psychopathology-based sample (NESDA), taking into account and additionally examining the role of (comorbid) anxiety disorders. Finally, the results of Chapter 2 through 9 are summarized, discussed and integrated with current knowledge in **Chapter 10**.

References

1. Kretschmer E. *Körperbau und Charakter (Physique and Character)*. Berlin, Germany: Springer; 1921.
2. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr.* 1956;4:20-34.
3. Butler J, Rodondi N, Zhu Y et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. *J Am Coll Cardiol.* 2006;47:1595-1602.
4. Dekker JM, Girman C, Rhodes T et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation.* 2005;112:666-673.
5. Holvoet P, Kritchevsky SB, Tracy RP et al. The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the health, aging, and body composition cohort. *Diabetes.* 2004;53:1068-1073.
6. Isomaa B, Almgren P, Tuomi T et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24:683-689.
7. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in beaver dam. *Diabetes Care.* 2002;25:1790-1794.
8. Lakka HM, Laaksonen DE, Lakka TA et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA.* 2002;288:2709-2716.
9. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. *BMJ.* 2006;332:878-882.
10. Patten SB, Williams JV, Lavorato DH, Campbell NR, Eliasziw M, Campbell TS. Major depression as a risk factor for high blood pressure: epidemiologic evidence from a national longitudinal study. *Psychosom Med.* 2009;71:273-279.
11. Atlantis E, Baker M. Obesity effects on depression: systematic review of epidemiological studies. *Int J Obes (Lond).* 2008;32:881-891.
12. Boyle SH, Surwit RS, Georgiades A et al. Depressive symptoms, race, and glucose concentrations: the role of cortisol as mediator. *Diabetes Care.* 2007;30:2484-2488.
13. Bjorntorp P. Heart and soul: stress and the metabolic syndrome. *Scand Cardiovasc J.* 2001;35:172-177.
14. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev.* 2001;2:73-86.
15. Vitaliano PP, Scanlan JM, Zhang J, Savage MV, Hirsch IB, Siegler IC. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosom Med.* 2002;64:418-435.
16. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci.* 2008;31:464-468.
17. Vreeburg SA, Hoogendijk WJ, van PJ et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry.* 2009;66:617-626.
18. Dekker MJ, Koper JW, van Aken MO et al. Salivary cortisol is related to atherosclerosis of carotid arteries. *J Clin Endocrinol Metab.* 2008;93:3741-3747.
19. Fraser R, Ingram MC, Anderson NH, Morrison C, Davies E, Connell JM. Cortisol effects on body mass, blood pressure, and cholesterol in the general population. *Hypertension.* 1999;33:1364-1368.
20. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry.* 1999;174:307-311.
21. Rijksinstituut voor Volksgezondheid en Milieu. Nationaal Kompas Volksgezondheid. *www nationaalkompas nl.* Accessed Sept 10, 2009.
22. World Health Organization. *www.who int.* Accessed Sept 10, 2009.

23. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3:e442.
24. *Diagnostic and statistical manual of mental disorders, fourth edition*. 4th ed. Washington, DC: American Psychiatric Association; 2001.
25. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry.* 1999;174:307-311.
26. Beekman AT, Deeg DJ, van Tilburg T, Smit JH, Hooijer C, van Tilburg W. Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord.* 1995;36:65-75.
27. Beekman AT, Bremmer MA, Deeg DJ et al. Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. *Int J Geriatr Psychiatry.* 1998;13:717-726.
28. Onrust SA, Cuijpers P. Mood and anxiety disorders in widowhood: a systematic review. *Aging Ment Health.* 2006;10:327-334.
29. van Grootheest DS, Beekman AT, Broese van Groenou MI, Deeg DJ. Sex differences in depression after widowhood. Do men suffer more? *Soc Psychiatry Psychiatr Epidemiol.* 1999;34:391-398.
30. Cacioppo JT, Hughes ME, Waite LJ, Hawkley LC, Thisted RA. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. *Psychol Aging.* 2006;21:140-151.
31. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med.* 2004;66:802-813.
32. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J.* 2006;27:2763-2774.
33. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med.* 2002;23:51-61.
34. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med.* 2003;65:201-210.
35. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry.* 2007;22:613-626.
36. van Melle JP, de JP, Spijkerman TA et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med.* 2004;66:814-822.
37. Lett HS, Blumenthal JA, Babyak MA, Strauman TJ, Robins C, Sherwood A. Social support and coronary heart disease: epidemiologic evidence and implications for treatment. *Psychosom Med.* 2005;67:869-878.
38. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes.* 1988;37:1595-1607.
39. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2005;28:2289-2304.
40. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation.* 2002;106:3143-3421.
41. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA.* 2002;287:356-359.
42. Dik MG, Jonker C, Comijs HC et al. Contribution of metabolic syndrome components to cognition in older individuals. *Diabetes Care.* 2007;30:2655-2660.
43. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992;267:1244-1252.

44. Whitworth JA, Williamson PM, Mangos G, Kelly JJ. Cardiovascular consequences of cortisol excess. *Vasc Health Risk Manag.* 2005;1:291-299.
45. Franchimont D, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH clinical staff conference. *Neuroimmunomodulation.* 2002;10:247-260.

Chapter 2

Psychosocial risk factors and the metabolic syndrome in elderly persons

Findings from the Health, Aging and Body Composition study

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Journal of Gerontology: Medical Sciences 2007; 62(5): 563-569

Abstract

Background

Psychosocial factors have been associated with metabolic abnormalities that increase the risk of cardiovascular disease and diabetes. This study investigated the cross-sectional relationship between psychosocial risk factors and the metabolic syndrome in a community-based sample of older persons.

Methods

Participants were 2917 persons aged 70-79 years enrolled in the Health, Aging and Body Composition study. Depressive and anxiety symptoms, negative life events, and inadequate emotional support were assessed, and a summary psychosocial risk index was calculated. Metabolic syndrome was defined as three or more of the following criteria: abdominal obesity, high triglycerides, low high-density lipoprotein cholesterol, high fasting glucose, and high blood pressure.

Results

Negative life events and inadequate emotional support increased the odds of having metabolic syndrome after adjustment for demographic and lifestyle variables (OR per life event = 1.13, 95% CI = 1.05-1.22; OR = 1.35, 95% CI = 1.10-1.66, respectively). The relationship between depressive symptoms and metabolic syndrome was only found in white (OR per SD = 1.11, 95% CI = 1.01-1.23), but not in black (OR per SD = 0.97, 95% CI = 0.86-1.11) persons. Anxiety symptoms were significantly associated with metabolic syndrome in men (OR per SD = 1.13, 95% CI = 1.00-1.28), but not in women (OR per SD = 0.98, 95% CI = 0.89-1.08). Moreover, a higher score on the psychosocial risk index was associated with an increased probability of having the metabolic syndrome (OR = 1.30, 95% CI = 1.12-1.52).

Conclusions

In the elderly population, different psychosocial risk factors are associated with a higher prevalence of the metabolic syndrome. Whether reduction or better management of psychosocial risk factors can improve the metabolic profile remains to be demonstrated.

Introduction

Cardiovascular disease (CVD), diabetes, and affective disorders rank high among the leading disorders causing distress, disability, and mortality.[1] There is increasing evidence that these disorders are linked and that clustering of these disorders presents one of the most challenging problems for public health, especially in later life. For instance, depression and anxiety have been shown to increase the risk of new CVD events, new coronary heart disease (CHD) events, and cardiac mortality.[2-4] Also, patients with newly diagnosed type 2 diabetes are more likely to have a history of depression than are people free of diabetes.[5] In addition to affective disorders, other stressors known to contribute to psychological distress have been associated with CVD and diabetes. Both lack of emotional support and experience of major stressful life events have been shown to subsequently increase the risk of CVD, CHD, and type 2 diabetes.[6-8] These findings suggest that, although depression, anxiety, emotional support, and stressful life events are distinct entities, they can all be seen as psychosocial risk factors for developing CVD or diabetes.

Emerging evidence suggests that part of the link between these psychosocial risk factors and CVD and diabetes may operate through the metabolic syndrome,[9] a clustering of several CVD risk factors including (i) abdominal obesity, (ii) hypertriglyceridemia, (iii) low high-density lipoprotein (HDL) cholesterol, (iv) hypertension, and (v) hyperglycemia. According to the National Cholesterol Education Program Adult Treatment Panel III, a person has the metabolic syndrome if three or more of these conditions are present.[10] Using these criteria, the Third National Health and Nutrition Examination Survey estimated a prevalence of 23.7% of the metabolic syndrome among all US adults, and a prevalence of 42.0% among adults aged 70 years and older.[11] A number of studies has shown that individuals with the metabolic syndrome have an increased risk of cardiovascular morbidity and mortality.[12-15] Furthermore, persons with metabolic abnormalities have shown an enlarged risk of incident diabetes, with increasing risks in those exhibiting more abnormalities.[15]

Psychosocial risk factors, which might include both exposure to stressors, e.g. life events, and experienced psychological distress, such as depression and anxiety, have been linked to individual components of the metabolic syndrome, including insulin resistance, high blood pressure, abdominal obesity, and lipid abnormalities.[8,16,17] Such a link could be due to the fact that psychological stress can result in sensitization of the hypothalamo-pituitary-adrenal (HPA) axis,[18,19] elevated inflammation,[20] and inhibition of sex steroid secretion,[21,22] all of which may induce metabolic abnormalities.[23-25] A combination of psychosocial risk factors might dysregulate these biological systems even more.

A first step in unraveling the relationship between psychosocial risk factors and the metabolic syndrome is to explore their cross-sectional association. In addition, it is important to know whether psychosocial risk factors co-occur with the metabolic syndrome. Treatment of both metabolic syndrome and psychosocial stress may be less effective if accompanying problems are ignored. Until now, few studies have examined the link between psychosocial risk factors and the metabolic syndrome directly, especially in old age. The present study investigates the association between psychosocial risk factors, as indicated by depression, anxiety, recent life events, and experienced inadequate emotional

support, and the metabolic syndrome in a large cohort of well-functioning older men and women.

Methods

Study population

Participants were from the Health, Aging and Body Composition (ABC) study, a prospective cohort study of 3075 well-functioning white and black elders, aged 70-79 years. Participants were recruited in 1997 and 1998, drawn from a sample of Medicare-eligible beneficiaries residing in the areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Individuals were excluded if they (i) were incapable of communicating, (ii) reported difficulty with walking for one-quarter mile, walking up 10 steps, or performing activities of daily living, (iii) had active cancer treatment in the past 3 years, or (iv) had plans to move out of the area. Baseline measurements were used for the present study. Baseline data on metabolic syndrome were missing for 40 participants, and 118 participants had missing data on psychosocial risk indicators, leaving 2917 participants for the present analysis. Persons with missing data were more often black than those in the present study ($p = .007$), but they did not differ in terms of age, sex, and education. All participants signed an informed written consent, approved by the institutional review boards of the clinical sites.

Measurements

Baseline characteristics

Demographic characteristics included age, sex, and race (white or black). Educational level was measured continuously on a scale from 1 (grade 1) to 18 (doctoral degree), indicating the highest level of education completed. Income was measured by dividing persons into yearly income groups: < $10,000, $10,000-$25,000, $25,000-$50,000, and ≥ $50,000. Because there were many missing values on this variable, missing value was included as a separate group. Furthermore, some lifestyle characteristics were assessed: smoking status (non-, former, or current), current alcohol intake (drinks > 1 drink per day or not), and physical activity (sum of weight training, high and medium intensity exercise, and aerobic dance [in kcal/kg/wk]). Baseline presence of CVD (including stroke or transient ischemic attack, myocardial infarction, angina pectoris, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting) and diabetes was adjudicated using standardized algorithms considering various sources of information: self-report, medication use, clinical examination findings, and medical claims data from the former Health Care Financing Administration.

Metabolic syndrome

Metabolic syndrome was defined, following the National Cholesterol Education Program Adult Treatment Panel III guidelines,[10] as meeting at least three of the following five criteria: (i) abdominal obesity (waist circumference > 102 cm in men and > 88 cm in women), (ii) hypertriglyceridemia (triglyceride level of ≥ 150 mg/dl), (iii) low HDL cholesterol (< 40 mg/dl in men and < 50 mg/dl in women), (iv) high blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or

currently using antihypertensive medication), (v) high fasting glucose (≥ 110 mg/dl or currently using antidiabetic medication). Waist circumference and blood pressure were both averaged over two measurements. All medication regularly taken in the past 2 weeks were brought in, recorded, and coded according to the Iowa Drug Information System.[26] Use of antidiabetic and antihypertensive drugs was ascertained from this inventory. Lipid and fasting glucose levels were measured after an overnight fast. In addition to presence of metabolic syndrome, in line with others,[27] the number of metabolic syndrome components was used as an index of severity of metabolic abnormalities.

Psychosocial risk factors

Depressive symptoms - Depressive symptoms were measured with the 20-item Center for Epidemiologic Studies Depression (CES-D) scale assessing depressive symptoms in the previous week.[28] This scale, ranging from 0 to 60, has been widely used in older populations and has been shown to be a valid instrument[29] (internal consistency was high: Cronbach alpha = 0.81).

Anxiety symptoms - Anxiety symptoms were measured using three items from the anxiety subscale of the validated Hopkins Symptom Checklist.[30] The items were: "During the past week, have you felt nervous or shaky inside?, … tense or keyed up? … fearful?" Possible responses were "no", "a little", "quite a bit", and "extremely". An anxiety symptoms score was calculated, ranging from 0 to 9, as used before.[31] The Cronbach alpha of these three items was 0.61.

Negative life events – The occurrence of seven common and important life events during the past year was assessed and summed. Life events included (i) close friend or family had a serious accident or illness, (ii) spouse or partner died, (iii) (grand)child, close friend, or relative died, (iv) pet died, (v) relationship with close friend or family changed for the worse, (vi) participant or family has been assaulted or robbed, and (vii) close friend or family has been arrested or in trouble with the law.

Inadequate emotional support - Participants who reported they could have used "some" or "a lot" more emotional support than they received in the past year were considered to have inadequate emotional support. This measure gives an indication of the subjective need for emotional support, which has been associated with the development and progression of CHD.[7]

Psychosocial risk index - The above four measures have all individually been shown to be psychosocial risk factors for developing CVD and diabetes.[2-8] Although little is known about the underlying biological mechanisms, it might be hypothesized that these psychosocial variables have a similar or, at least to some extent, an additive biological impact. In consequence, it might be that persons who have high scores on more than one psychosocial risk factor have an even greater biological dysregulation and therefore are even more at risk for developing the metabolic syndrome, CVD or diabetes. Therefore, the above psychosocial

factors were combined to calculate a summary psychosocial risk index. Depressive symptoms were standardized into a continuous variable ranging from 0 to 1 by dividing each individual score by the maximum possible CES-D score (i.e. 60). Similar standardization was done for anxiety symptoms (divided by 9) and life events (divided by 7). Inadequate emotional support was kept as a dichotomous 0-1 measure. Then, the four 0-1 measures were summed to attain an overall continuous psychosocial risk index, ranging from 0 to 4. The four psychosocial risk factors were associated with each other (all $p < .001$): the highest correlation was found between depression and anxiety (Spearman correlation = 0.40), and the lowest correlations were found with negative life events (between 0.09 and 0.14).

Statistical analysis

Chi-square and t test statistics were used to assess differences in psychosocial risk factors between participants with or without metabolic syndrome and with or without a metabolic abnormality. For all following analyses, age, sex, race, education, income, smoking status, alcohol intake, and physical activity were used as covariates. Logistic regression analyses were conducted to assess the association between metabolic syndrome and each of the psychosocial risk factors. Because a few studies reported sex differences in the link between psychosocial risk factors and cardiovascular outcomes,[2,32] sex interactions were explored and also race interactions were tested. To examine if there was a linear relationship between psychosocial risk factors and number of metabolic syndrome components, linear regression was used. To test whether psychosocial risk factors were independently associated with the metabolic syndrome, a logistic regression analysis was conducted including all four psychosocial risk factors at the same time. Furthermore, we checked whether the link between psychosocial risk factors and metabolic syndrome was dependent on the presence of CVD or diabetes by testing for interactions with CVD or diabetes, respectively. In addition, we ran stratified analyses for persons with and without CVD.

Results

Baseline characteristics of the study population are shown in Table 1. The mean age of the 2917 participants included in this study was 73.6 years (SD = 2.9); 51.5% were women, 41.1% were black, and 38.6% of the participants had the metabolic syndrome. Overall, levels of psychosocial risk were low.

As shown in Table 2, metabolic syndrome was associated with depressive symptoms, negative life events, inadequate emotional support, and the psychosocial risk index. Furthermore, although levels of psychosocial risk were rather low for the total sample, in general they appeared to be somewhat higher in participants with metabolic abnormalities, although differences were small and only some were statistically significant.

We then conducted logistic regression analyses to calculate the odds ratio (OR) of metabolic syndrome for the different psychosocial risk factors before and after adjustment (Table 3). Also, sex and race interactions were explored by examining sex and race by psychosocial risk factor interaction terms. Before adjustment, depressive symptoms modestly increased the odds of the metabolic syndrome, but this was no longer significant

Table 1. Baseline characteristics

Characteristic	*N = 2917*
Age (years), mean (SD)	73.6 (2.9)
Female, %	51.5
Black, %	41.1
Education, mean (SD)	13.0 (3.2)
Family income, %	
< $ 10,000	11.7
$ 10,000 - $ 25,000	34.0
$ 25,000 - $ 50,000	28.1
≥ $ 50,000	14.2
Missing	12.1
Smoking status, %	
Nonsmoker	43.7
Former smoker	46.1
Current smoker	10.1
> 1 Alcoholic drink per day, %	7.4
Physical activity (kcal/kg/week), mean (SD)	6.2 (15.9)
Baseline cardiovascular disease, %	24.0
Baseline diabetes, %	15.2
Psychosocial risk factors	
Depressive symptoms score (0-60), mean (SD)	4.7 (5.3)
Anxiety symptoms score (0-9), mean (SD)	0.66 (1.2)
Negative life events in the past year (0-7), mean (SD)	1.1 (1.0)
Inadequate emotional support, %	15.4
Psychosocial risk index (0-4), mean (SD)	0.47 (0.5)
Metabolic syndrome	
Abdominal obesity, %	60.9
High triglycerides, %	30.7
Low high-density lipoprotein cholesterol, %	29.4
High fasting glucose, %	24.0
High blood pressure, %	79.1
Metabolic syndrome, %	38.6
Number of metabolic components (0-5), mean (SD)	2.2 (1.2)
0, %	5.9
1, %	23.6
2, %	32.0
3, %	21.9
4, %	12.5
5, %	4.1

Table 2. Association between psychosocial risk factors and metabolic syndrome in older men and women

N = 2917	***Abdominal obesity***		***High triglycerides***		***Low HDL cholesterol***	
Psychosocial risk factor	No	Yes	No	Yes	No	Yes
Depressive symptoms score, mean (SD)	4.5 (5.1)	4.8 [b] (5.4)	4.6 (5.2)	4.9 (5.5)	4.7 (5.3)	4.8 (5.3)
Anxiety symptoms score, mean (SD)	0.63 (1.2)	0.68 (1.2)	0.63 (1.2)	0.73 [a] (1.3)	0.66 (1.2)	0.67 (1.2)
Negative life events, mean (SD)	1.1 (1.0)	1.2 (1.0)	1.1 (1.0)	1.2 [a] (1.0)	1.1 (1.0)	1.2 (1.0)
Inadequate emotional support, %	13.6	16.6 [a]	14.7	16.9	15.2	15.9
Psychosocial risk index, mean (SD)	0.44 (0.5)	0.48 [a] (0.5)	0.45 (0.5)	0.50 [a] (0.5)	0.46 (0.5)	0.48 (0.5)
	High blood pressure		***High fasting glucose***		***Metabolic syndrome [c]***	
Psychosocial risk factor	No	Yes	No	Yes	No	Yes
Depressive symptoms score, mean (SD)	4.3 (4.8)	4.8 [a] (5.4)	4.7 (5.2)	4.7 (5.7)	4.5 (5.0)	4.9 [a] (5.7)
Anxiety symptoms score, mean (SD)	0.66 (1.2)	0.66 (1.2)	0.65 (1.2)	0.70 (1.2)	0.64 (1.2)	0.70 (1.2)
Negative life events, mean (SD)	1.1 (1.0)	1.1 (1.0)	1.1 (1.0)	1.2 (1.0)	1.1 (1.0)	1.2 [a] (1.0)
Inadequate emotional support, %	13.6	15.9	14.3	18.7 [a]	13.8	18.0 [a]
Psychosocial risk index, mean (SD)	0.44 (0.5)	0.48 [b] (0.5)	0.45 (0.5)	0.51 [a] (0.5)	0.44 (0.5)	0.51 [a] (0.5)

HDL = high-density lipoprotein. [a] $p \leq .05$ (yes versus no) [b] $p \leq .10$ (yes versus no), based on X^2 tests for dichotomous variables and independent t tests for continuous variables; [c] metabolic syndrome: ≥ 3 of the following criteria: abdominal obesity, high triglycerides, low HDL cholesterol, high fasting glucose, high blood pressure.

after adjustment (OR per SD increase = 1.06, 95% CI = 0.98-1.14, p = .16). However, a trend was found for a race by depressive symptoms interaction (p = .10): the odds of metabolic syndrome increased with increases in depressive symptoms in white (OR per SD increase = 1.11, 95% CI = 1.01-1.23, p = .03), but not in black (OR per SD increase = 0.97, 95% CI = 0.86-1.11, p = .67) persons. Although there was no overall increase in odds of metabolic syndrome with increases of anxiety symptoms (OR per SD increase = 1.03, 95% CI = 0.96-1.11, p = .44), a trend for a sex by anxiety symptoms interaction was identified (p = .08). Men had a 13% increased odds of metabolic syndrome per SD

Table 3. Association between psychosocial risk factors and metabolic syndrome and number of metabolic abnormalities

N = 2917	***Metabolic Syndrome*** [a]								
	Unadjusted			Adjusted [c]			Adjusted [d]		
Psychosocial risk factor	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Depressive symptoms score [e f]	1.08	1.00-1.16	.04	1.05	0.98-1.13	.20	1.01	0.93-1.11	.78
Whites (N = 1718)	*1.15*	*1.05-1.26*	*.003*	*1.11*	*1.01-1.23*	*.03*	*1.10*	*0.98-1.23*	*.11*
Blacks (N = 1199)	*0.97*	*0.86-1.10*	*.67*	*0.97*	*0.86-1.11*	*.67*	*0.91*	*0.79-1.05*	*.21*
Anxiety symptoms score [e g]	1.06	0.98-1.14	.15	1.03	0.96-1.11	.44	0.99	0.91-1.08	.78
Men (N = 1416)	*1.13*	*1.00-1.27*	*.05*	*1.13*	*1.00-1.28*	*.05*	*1.08*	*0.94-1.24*	*.26*
Women (N = 1501)	*0.98*	*0.89-1.08*	*.73*	*0.98*	*0.89-1.08*	*.73*	*0.94*	*0.84-1.05*	*.25*
Negative life events	1.12	1.04-1.21	.003	1.13	1.05-1.22	.001	1.12	1.04-1.21	.004
Inadequate emotional support	1.37	1.12-1.68	.002	1.35	1.10-1.66	.005	1.31	1.05-1.62	.02
Psychosocial risk index	1.34	1.15-1.55	<.001	1.30	1.12-1.52	.001			
	Number of Abnormalities [b]								
	Unadjusted			Adjusted [c]			Adjusted [d]		
Psychosocial risk factor	β	p		β	p		β	p	
Depressive symptoms score [e f]	.043	.02		.021	.25		.004	.84	
Whites (N = 1718)	*.069*	*.004*		*.043*	*.08*		*.026*	*.37*	
Blacks (N = 1199)	*-.001*	*.98*		*-.005*	*.86*		*-.020*	*.54*	
Anxiety symptoms score [e g]	.031	.10		.014	.44		-.002	.92	
Men (N = 1416)	*.060*	*.02*		*.058*	*.03*		*.051*	*.09*	
Women (N = 1501)	*-.019*	*.46*		*-.016*	*.52*		*-.045*	*.13*	
Negative life events	.039	.03		.043	.02		.039	.04	
Inadequate emotional support	.056	.003		.047	.01		.043	.03	
Psychosocial risk index	.068	<.001		.052	.005				

[a] Based on logistic regression analyses; [b] based on linear regression analyses; [c] adjusted for age, sex, race, education, income, smoking status, alcohol intake and physical activity; [d] additionally adjusted for other psychosocial risk factors; [e] OR per SD increase: for depressive symptoms SD = 5.3, for anxiety symptoms SD = 1.2; [f] a trend for race interaction was observed with depressive symptoms: for metabolic syndrome p = .10, for number of abnormalities p = .19; [g] a (trend for) sex interaction was observed with anxiety symptoms: for metabolic syndrome p = .08, for number of abnormalities p = .03.

increase in anxiety symptoms score (OR = 1.13, 95% CI = 1.00-1.28, p = .05). For women, anxiety symptoms did not elevate the odds of metabolic syndrome (OR per SD increase = 0.98, 95% CI = 0.89-1.08, p = .73). Experiencing a negative life event did increase the odds of metabolic syndrome by 13% (OR = 1.13, 95% CI = 1.05-1.22), p = .001). Also, people who experienced inadequate emotional support had a 35% increased odds of having the metabolic syndrome (OR = 1.35, 95% CI = 1.10-1.66, p = .005) compared to people with adequate emotional support. Furthermore, when the four psychosocial risk factors were

Table 4. Association between psychosocial risk factors and metabolic syndrome

	No CVD			***Prevalent CVD***		
	N = 2216			*N = 701*		
Psychosocial risk factor	OR [a]	95% CI	p	OR [a]	95% CI	p
Depressive symptoms score [b]	1.07	0.98-1.17	.14	0.98	0.84-1.13	.75
Whites	*1.13*	*1.02-1.27*	*.03*	*1.04*	*0.85-1.26*	*.74*
Blacks	*0.98*	*0.84-1.14*	*.78*	*0.93*	*0.74-1.17*	*.54*
Anxiety symptoms score [b]	1.02	0.93-1.11	.75	1.04	0.89-1.21	.66
Men	*1.13*	*0.97-1.32*	*.11*	*1.04*	*0.83-1.29*	*.74*
Women	*0.97*	*0.87-1.08*	*.52*	*1.03*	*0.83-1.28*	*.79*
Negative life events	1.13	1.04-1.24	.006	1.10	0.94-1.29	.22
Inadequate emotional support	1.33	1.04-1.69	.02	1.39	0.93-2.10	.11
Psychosocial risk index	1.29	1.08-1.54	.005	1.28	0.94-1.74	.11

CVD = cardiovascular disease. [a] Based on logistic regression adjusted for age, sex, race, education, income, smoking status, alcohol intake and physical activity; [b] OR per SD increase: for depressive symptoms SD = 5.3, for anxiety symptoms SD = 1.2.

combined into one overall psychosocial risk index, the odds of metabolic syndrome was 1.30 times higher per point increase on the psychosocial risk index (95% CI = 1.12-1.52, p = .001). For the index, no statistically significant sex or race interactions were found (all p > .15). The results of the linear regression analyses of the relationship between psychosocial risk factors and number of metabolic abnormalities are also shown in Table 3 and are in line with the results for the dichotomous measure of metabolic syndrome.

When all psychosocial risk factors were included in the same model, it appeared that negative life events and inadequate emotional support were still independently associated with the metabolic syndrome (OR = 1.12, 95% CI = 1.04-1.21, p = .004 and OR = 1.31, 95% CI = 1.05-1.62, p = .02, respectively). In contrast, associations for depressive and anxiety symptoms were weakened and no longer statistically significant, although there was a trend for association between depressive symptoms and the metabolic syndrome in whites (OR = 1.10, 95% CI = 0.98-1.23, p = .11) and between anxiety symptoms and number of metabolic abnormalities in men (β = .051, p = .09).

Table 4 shows the results of logistic regression analyses testing the association between psychosocial risk factors and the metabolic syndrome, stratified by prevalent CVD status. The prevalence of the metabolic syndrome was 36.4% among persons without CVD (N = 2216) and 45.5% among those with CVD (N = 701). Among persons without CVD, the link between psychosocial risk factors and the metabolic syndrome was very similar as compared to the overall sample, and was significant for depressive symptoms in whites (p = .03), negative life events (p = .006), inadequate emotional support (p = .02), and the psychosocial risk index (p = .005). There was no evidence for a CVD by psychosocial risk factor interaction (all $p_{interaction} > .15$). No diabetes by psychosocial risk factor interaction was found either (all $p_{interaction} > .15$).

Discussion

This study showed that distinct psychosocial risk factors were associated with the metabolic syndrome in a large cohort of well-functioning older persons. We found that older people who experienced negative life events and inadequate emotional support had an increased prevalence of the metabolic syndrome. For depression, an association with the metabolic syndrome was found only in whites and not in blacks. Anxiety symptoms appeared to be associated with the metabolic syndrome in men, but not in women. Furthermore, when these psychosocial factors were combined into a psychosocial risk index, persons with a higher risk index had a higher probability of having the metabolic syndrome.

Our study is one of the first to test the relationship between different psychosocial risk factors and the metabolic syndrome in a population-based cohort of older people. Most studies so far have examined the association between psychosocial factors and the metabolic syndrome indirectly, by studying individual metabolic components. Only few studies were able to test this relationship directly. Räikkönen and colleagues[33] reported an association between depressive symptoms, tension, and anger and the metabolic syndrome in a population-based cohort of 425 middle-aged women. Kinder and colleagues[34] found that young women, but not men, with a history of depression were twice as likely to have the metabolic syndrome. In our study, a psychosocial risk index including depressive and anxiety symptoms, negative life events, and inadequate emotional support showed a linear relationship with the odds of having the metabolic syndrome. This finding suggests that persons with high values on these measures have a higher risk for the metabolic syndrome. However, strongest associations with the metabolic syndrome were found for negative life events and inadequate emotional support, and these associations appeared to be independent of the associations of other psychosocial risk factors. Associations between depressive and anxiety symptoms and the metabolic syndrome were modest and not consistent across race and sex.

In addition, the results of our study show that associations between psychosocial risk factors and the metabolic syndrome seemed more consistent than the associations with individual components of the metabolic syndrome. These results may suggest that psychosocial risk factors may lead to not just one metabolic abnormality, but have a more widespread effect on metabolism and lead to a cluster of metabolic abnormalities, such as present in the metabolic syndrome. Furthermore, our results show that the relationship between psychosocial risk factors and the metabolic syndrome is not due to presence of CVD. When CVD patients were excluded, the found associations remained, which indicates that the link between psychosocial risk factors and the metabolic syndrome in our study does not just reflect a consequence of underlying clinical CVD.

In our study, a trend for a race interaction for depressive symptoms was found. This finding is in contradiction to those in the study of Kinder and colleagues[34] where no interaction for race was found. Furthermore, we found a trend for sex interaction for anxiety, which has not been described before. The prevalence of most psychosocial risk factors was rather similar for whites versus blacks and only slightly higher for women than for men, indicating that differences in prevalence cannot explain the interaction effects observed. Because we had a large study sample and only found trends for interaction, these

may be chance findings and further research should confirm and explain the interaction effects observed in this research.

There may be different pathways through which psychosocial risk factors are related to the metabolic syndrome and, although the psychosocial risk factors used in this study are rather distinct concepts, these pathways may be similar. Psychosocial factors have shown to activate the HPA axis resulting in higher cortisol concentrations[18,19] which, in turn, are associated with metabolic abnormalities such as obesity, insulin resistance, and high blood pressure.[35] Another pathway may be through inflammatory processes. Psychosocial risk factors, especially depression, have shown to be associated with increased levels of inflammatory markers, such as interleukin-6 and C-reactive protein.[20] Inflammatory markers have been linked to obesity, lower HDL cholesterol levels, and higher triglycerides and fasting glucose concentrations.[24] A third pathway could be through sex steroid hormones, as low levels of testosterone and dehydroepiandrosterone sulfate (DHEA-S) have been associated with major depression.[21,22] Alternatively, low levels of sex steroid hormones have been linked to various metabolic abnormalities.[25] However, evidence for these pathways remains indirect, and additional longitudinal research is needed to investigate these processes further. In addition to these biological pathways, it may be that people with a high psychosocial risk have poorer health habits, e.g. they exercise less or have more fat intake, thereby increasing their metabolic risk.[9] However, we did adjust for some lifestyle variables; this adjustment did not affect the results much.

Our study has some limitations. First, causal inferences are limited due to the cross-sectional design. A longitudinal design would be more appropriate to explore the direction of the relationship between psychological distress and the metabolic syndrome. However, in our study, metabolic syndrome was only remeasured after 5 years. Due to dropout (15%), missing values (19%), and exclusion of persons with baseline metabolic syndrome (27%), there was only a limited and likely very selective subsample left for longitudinal analyses. In addition, due to aging and frailty processes among the oldest old, several counteractive body composition changes exist (e.g. loss of fat mass), which could contaminate a possibly existing link between psychosocial risk factors and incidence of metabolic syndrome. Consequently, a longitudinal approach that examines the incidence of metabolic syndrome may be better studied in a younger cohort where frailty and selective survival play no major role yet. What can be said about causality is that, in our study, one of the strongest associations with metabolic syndrome was found for negative life events in the past year, which generally have a rather random and independent occurrence (e.g. death or illness of family member, violence, relative in trouble with the law). Consequently, for this association, the most likely pathway is that exposure to negative life events is associated with unfavorable metabolic changes. A second limitation is that our population was relatively healthy, with a low prevalence of depressive symptoms. The mean CES-D score was 4.7, and only 4.6% met the CES-D cutoff of 16 for clinically relevant depression. This percentage is low compared to other elder population-based studies (between 10 and 15%).[3,36] Restriction of range in the markers for psychosocial risk may have weakened the associations found. However, despite this limitation an association with the metabolic syndrome was found. Our study also had some important strengths, including the access to

a large cohort of elderly persons from the community, allowing sufficient statistical power to examine the association between psychosocial risk factors and the metabolic syndrome and allowing exploration of sex and race differences. Furthermore, both psychosocial risk and the metabolic syndrome were examined in detail, allowing assessment of associations of components of both. Moreover, a well-accepted definition of the metabolic syndrome was used, enhancing the comprehensibility and interpretability of our results.

We believe that our findings support the idea that there is an important relationship between a variety of psychosocial risk factors and the metabolic syndrome, which are both common in later life. These results contribute significantly to the recent discussion implicating pathways from psychosocial factors through the metabolic syndrome to CVD and diabetes. A next step would be to test the hypothesis as to the mechanisms underlying the link between psychosocial risk factors and the metabolic syndrome. Knowing these mechanisms may lead to more effective and integrated efforts to prevent and treat cardiovascular disorders, diabetes, depression, and anxiety, which co-occur in later life.

Acknowledgements

This work was supported by National Institute on Aging (NIA) contract numbers N01-AG-6-2101, N01-AG-2103, and N01-AG-6-2106 and in part by the Intramural Research Program of the National Institutes of Health, NIA. Data analyses were supported by grant 1R01-HL72972 from the National Heart, Lung, and Blood Institute (NHLBI).

References

1. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet.* 1997;349:1436-1442.
2. Penninx BW, Guralnik JM, Mendes de Leon CF et al. Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age. *Am J Cardiol.* 1998;81:988-994.
3. Penninx BW, Beekman AT, Honig A et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry.* 2001;58:221-227.
4. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation.* 2005;111:480-487.
5. Brown LC, Majumdar SR, Newman SC, Johnson JA. History of depression increases risk of type 2 diabetes in younger adults. *Diabetes Care.* 2005;28:1063-1067.
6. Berkman LF, Leo-Summers L, Horwitz RI. Emotional support and survival after myocardial infarction. A prospective, population-based study of the elderly. *Ann Intern Med.* 1992;117:1003-1009.
7. Lett HS, Blumenthal JA, Babyak MA, Strauman TJ, Robins C, Sherwood A. Social support and coronary heart disease: epidemiologic evidence and implications for treatment. *Psychosom Med.* 2005;67:869-878.
8. Mooy JM, de Vries H, Grootenhuis PA, Bouter LM, Heine RJ. Major stressful life events in relation to prevalence of undetected type 2 diabetes: the Hoorn Study. *Diabetes Care.* 2000;23:197-201.
9. Vitaliano PP, Scanlan JM, Zhang J, Savage MV, Hirsch IB, Siegler IC. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosom Med.* 2002;64:418-435.
10. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation.* 2002;106:3143-3421.

11. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA.* 2002;287:356-359.
12. Isomaa B, Almgren P, Tuomi T et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24:683-689.
13. Butler J, Rodondi N, Zhu Y et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. *J Am Coll Cardiol.* 2006;47:1595-1602.
14. Holvoet P, Kritchevsky SB, Tracy RP et al. The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the health, aging, and body composition cohort. *Diabetes.* 2004;53:1068-1073.
15. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in beaver dam. *Diabetes Care.* 2002;25:1790-1794.
16. Weber-Hamann B, Hentschel F, Kniest A et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. *Psychosom Med.* 2002;64:274-277.
17. Raikkonen K, Keltikangas-Jarvinen L, Adlercreutz H, Hautanen A. Psychosocial stress and the insulin resistance syndrome. *Metabolism.* 1996;45:1533-1538.
18. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992;267:1244-1252.
19. Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *J Affect Disord.* 2001;62:77-91.
20. Penninx BW, Kritchevsky SB, Yaffe K et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiatry.* 2003;54:566-572.
21. Schweiger U, Deuschle M, Weber B et al. Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. *Psychosom Med.* 1999;61:292-296.
22. Barrett-Connor E, von Muhlen D, Laughlin GA, Kripke A. Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study. *J Am Geriatr Soc.* 1999;47:685-691.
23. Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. *Psychoneuroendocrinology.* 2005;30:1-10.
24. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol.* 1999;19:972-978.
25. Haffner SM, Valdez RA, Mykkanen L, Stern MP, Katz MS. Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. *Metabolism.* 1994;43:599-603.
26. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol.* 1994;10:405-411.
27. Yaffe K, Kanaya A, Lindquist K et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA.* 2004;292:2237-2242.
28. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.
29. Beekman AT, Deeg DJ, van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med.* 1997;27:231-235.
30. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci.* 1974;19:1-15.
31. Mehta KM, Simonsick EM, Penninx BW et al. Prevalence and correlates of anxiety symptoms in well-functioning older adults: findings from the health aging and body composition study. *J Am Geriatr Soc.* 2003;51:499-504.

32. Penninx BW, Geerlings SW, Deeg DJ, van Eijk JT, van Tilburg W, Beekman AT. Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry.* 1999;56:889-895.
33. Raikkonen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? *Metabolism.* 2002;51:1573-1577.
34. Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom Med.* 2004;66:316-322.
35. Bjorntorp P, Rosmond R. Hypothalamic origin of the metabolic syndrome X. *Ann N Y Acad Sci.* 1999;892:297-307.
36. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry.* 1999;174:307-311.

Chapter 3

Hypercortisolemic depression is associated with the metabolic syndrome in late-life

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Psychoneuroendocrinology 2007; 32(2): 151-159

Abstract

Introduction

Depression has been hypothesized to be associated with metabolic abnormalities which increase the risk of cardiovascular disease and diabetes. Such a link could be due to increased HPA-axis activity. This study investigates the cross-sectional relationship between depression, urinary cortisol and metabolic syndrome in an older population.

Methods

Data are from 867 participants of the InCHIANTI study, aged ≥ 65 years. Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression (CES-D) scale; cortisol levels were determined in 24-h urine samples. Metabolic syndrome was defined as three or more of the following: abdominal obesity, high triglycerides, low high-density lipoprotein cholesterol, high blood pressure, and high fasting glucose.

Results

Clinically relevant depressed mood (CES-D ≥ 20) was present in 20.6% of the sample, and 24.5% had the metabolic syndrome. After adjustment for sociodemographics and health indicators, depression score (per SD increase: OR = 1.20, 95% CI = 1.02-1.41) and urinary cortisol level (per SD increase: OR = 1.23, 95% CI = 1.01-1.51) were significantly associated with presence of metabolic syndrome. There was, however, a significant interaction (p = .003) between depressed mood and urinary cortisol in the probability of having metabolic syndrome. The odds of metabolic syndrome in persons with both depressed mood and urinary cortisol excretion in the highest tertile were 1.84 (95% CI = 1.02-3.34) times increased compared to persons with neither condition.

Discussion

This study suggests a synergistic relationship between depression, cortisol and metabolic syndrome. Hypercortisolemic depression may constitute a specific risk group for the metabolic syndrome.

Introduction

There is growing evidence that depression may cause major life-threatening and disabling diseases, such as cardiovascular disease (CVD) and diabetes mellitus.[1-4] Recent studies suggest that the link between depression and CVD and diabetes may operate through the metabolic syndrome.[5] The metabolic syndrome is a clustering of risk factors associated with a particularly high risk of cardiovascular events and diabetes, and includes at least three of the following conditions: abdominal obesity, high triglyceride levels, low high-density lipoprotein (HDL) cholesterol, high blood pressure, and high levels of fasting glucose.[6] The estimated prevalence of the metabolic syndrome is as high as 42% in adults aged 60 years and over.[7]

Depression has been linked to metabolic abnormalities, such as abdominal obesity, high blood pressure and insulin resistance.[8-10] Several pathways for these links have been suggested. Vitaliano et al.[5] proposed that chronic stress causes depression and successive poor health habits that can lead to the metabolic syndrome and subsequent coronary heart disease. On the other hand more biological mechanisms have been proposed.[11] Probably one of the most important biological mechanisms is the dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis, of which cortisol is an essential component. Dysregulation of the HPA-axis is typically associated with chronic stress and a number of studies have described an association between depression and high cortisol levels[12,13] and, in turn, elevated levels of cortisol have been related to metabolic syndrome components such as abdominal obesity and glucose intolerance.[14] Although a few studies have examined the link between depression and individual components of the metabolic syndrome, there is little research on the extent to which depressive symptoms correlate with the metabolic syndrome as a whole, and the role of cortisol in this link. A study by Weber-Hamann et al.[10] among 45 older women found that hypercortisolemic depression, compared to normocortisolemic depression, was associated with increased visceral fat, indicating the importance of considering cortisol levels when examining the link between depression and metabolic abnormalities and suggesting that associations with metabolic abnormalities may be especially powerful for hypercortisolemic depression.

The present study uses data from a large sample of community-dwelling older persons to investigate the associations between depressive symptoms and urinary cortisol levels with metabolic syndrome and its components. We hypothesize that higher depressive symptoms and higher levels of cortisol are associated with metabolic syndrome and its components. In addition, the existence of an interaction between depressive symptoms and cortisol levels on the presence of metabolic syndrome will be explored, since we hypothesize that hypercortisolemic depression in particular will be linked to metabolic syndrome.

Methods

Study population

Participants were part of the InCHIANTI study, a prospective population-based study of older persons. In 1998 and 1999, the study sample was randomly selected from the population registry of two sites in Italy: Greve in Chianti, and Bagno a Ripoli, using a multistage stratified sampling method. Data collection consisted of a home interview, a 24-h

urine collection and a medical evaluation at the study clinic, which took place within 21 days after the home interview. The Italian National Institute of Research and Care on Aging ethical committee approved the study protocol and all respondents signed informed consent. A more detailed description of the study design is given elsewhere.[15]

The InCHIANTI study included 1155 participants aged 65 and over, but because of missing data on depressive symptoms (N = 76), metabolic syndrome (N = 101), urinary cortisol (N = 51), or incomplete (< 20 h) urine collection (N = 60), the present analysis included data from 867 participants. Excluded persons were significantly older (79.4 versus 74.1, $p < .001$), more often women (61.8% versus 55.0%, $p = .04$), and had less years of education (4.7 versus 5.5, $p = .002$).

Metabolic Syndrome

Metabolic syndrome was defined as the presence of three or more of the following criteria: (i) abdominal obesity (waist circumference > 102 cm in men or > 88 cm in women); (ii) hypertriglyceridemia (triglyceride level ≥ 150 mg/dl); (iii) low HDL cholesterol (< 40 mg/dl in men or < 50 mg/dl in women); (iv) high blood pressure (systolic/diastolic blood pressure ≥160/90 mmHg, and/or currently using anti-hypertensive medication); (v) high fasting glucose (≥ 110 mg/dl and/or currently using anti-diabetic medication). These criteria are similar to those outlined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III,[6] with a minor modification for hypertension. Ninety-two percent of the InCHIANTI respondents met the original blood pressure criterion (130/85 mmHg). In order to take into account the characteristics of the older study population and to only classify those participants who were definitively hypertensive the diagnostic cutoff was raised to 160/90 mmHg as done in other aging studies.[16]

During the medical evaluation, after a fasting period of at least 8 h, a 60-ml blood sample was drawn, stored in cold glass tubes, and delivered within 2 h to a central laboratory. Serum glucose, HDL cholesterol, and triglycerides were measured by standard laboratory methods. Waist circumference was measured by trained examiners at the largest mid-body point. Three blood pressure measurements were taken using a standard mercury sphygmomanometer with the respondent in a supine position; the average of the last two readings was used in this analysis. Drugs taken in the previous two weeks were identified and coded using the Anatomical Therapeutic Chemical (ATC) system to ascertain anti-diabetic and anti-hypertensive medication use. In addition to a dichotomous indicator of the metabolic syndrome, analyses were also conducted with continuous measures of metabolic syndrome components in order to investigate the consistency over and the importance of individual components. To incorporate medication use into the continuous metabolic syndrome component measures, 10 and 5 mmHg was added to systolic and diastolic blood pressure, respectively, for persons using antihypertensive medication since these values represent the average decline in blood pressure in antihypertensive medication trials.[17,18] Similarly, persons who used anti-diabetic medication and had a glucose level below 126 mg/dl, were given a value of 126 for fasting glucose.

Urinary Cortisol

The assessment of urinary cortisol over a 24-h period provides a rather stable indicator of the total cortisol excretion by the adrenals and measures the biologically active (unbound) cortisol. Before the in-clinic assessment, study participants were asked to collect all urine produced during a 24-h period starting after the first voided urine following awakening and including the first voided urine on the following day. At assessment, 10 ml aliquots of urine were prepared and stored at -80°C for later assaying at the Clinical Chemistry Laboratory of the Careggi Hospital, Italy. Urinary cortisol was measured by an immunochemiluminescence method and an ADVIA-Centaur immunoassay system (Bayer Diagnostics). The intra-assay coefficient of variation was less then 2.0% and the inter-assay coefficient of variation was less then 3.0%. Urinary cortisol level was defined as micrograms of cortisol excreted over 24 h. Both a continuous measure and a tertile categorization of urinary cortisol were used in the present study.

Depressive Symptoms

Depressive symptoms were assessed using the original 20-item version of the Center for Epidemiologic Studies-Depression Scale (CES-D) administered during the home interview.[19] The CES-D is a self-report scale, ranging from 0 to 60, which has been shown to be a valid instrument for identifying depressive symptoms in older community-dwelling adults[20] also in an Italian sample.[21] In our study, the internal consistency was high: Cronbach alpha = 0.82. Analyses were performed with both the continuous CES-D score (referred to as depressive symptoms) as well as a dichotomous indicator for clinically relevant depressed mood (CES-D ≥ 20; referred to as depressed mood). Normally, a cutoff score of 16 on the CES-D is considered to represent clinically relevant depression; however, previous studies have demonstrated that a cutoff of 20 on the CES-D avoids overestimation in older adult populations.[1,22,23]

Covariates

Covariates included sociodemographic variables (age, sex, and years of education), smoking status (non-, former, or current smoker) and current alcohol intake (yes or no 3 or more drinks a day). Number of chronic diseases (including cancer, liver disease, gastrointestinal disease, congestive heart failure, Parkinson's disease, peripheral arterial disease, lung disease, hip fracture, herniated disc, arthritis, osteoporosis and dementia) was calculated as a global indicator of poor physical health. Serum creatinine, measured through a modified Jaffe method, was used to calculate creatinine clearance with the Cockcroft-Gault formula. Following K/DOQI guidelines,[24] a creatinine clearance rate of 30 ml/min or lower was considered to indicate severe renal function impairment, which may profoundly disturb urinary cortisol levels. Identification of CVD (including angina pectoris, myocardial infarction, stroke or transient ischemic attack) and diabetes was based on a standardized algorithm using information on self-reported history, pharmacological treatments, medical exam data, and hospital discharge records. Use of corticosteroids, antidepressants, and benzodiazepines was assessed and coded according to ATC-codes.

Statistical Analyses

Baseline characteristics were compared across depression status using X^2 and t-test statistics. Logistic regression analyses, adjusted for age, sex, education, smoking status, alcohol intake, number of chronic diseases, severe renal function impairment, and urine volume (analyses with cortisol only), were conducted to independently assess the association between depression and urinary cortisol variables with metabolic syndrome. To examine whether the relationship between depression and metabolic syndrome is (partially) mediated by urinary cortisol, analyses including both cortisol and depression variables were conducted as well. For the latter, both a linear variable and the squared term for urinary cortisol were used, because earlier findings in this study sample[25] found a U-shaped association between depression and urinary cortisol, which was best described by a linear and squared term for urinary cortisol. In addition, since we hypothesized that especially hypercortisolemic depression could be associated with the metabolic syndrome, we tested for interaction between depressed mood and urinary cortisol by entering a depressed mood by cortisol interaction term.

Since sex differences in the relationship between depression and CVD have been observed before,[1,26] sex interactions were explored by entering sex by depression/cortisol interaction terms in adjusted models. In addition, it was explored whether associations were different for persons with and without already existing CVD or diabetes by exploring CVD/diabetes by depression/cortisol interaction terms. Finally, in order to examine whether associations with depression and cortisol variables were consistent for individual metabolic syndrome components, adjusted linear regression analyses were conducted with continuous variables for all five components as the outcomes. For these analyses, triglycerides, HDL cholesterol, and fasting glucose were log-transformed in order to normalize distributions.

Results

The mean age of the participants included in these analyses was 74.1 years (SD = 6.6) and 55.0% of the participants were women. 20.6% were depressed (CES-D ≥ 20) and 24.5% had the metabolic syndrome. The mean urinary cortisol level was 98.8 µg per 24 h (SD = 48.1). As shown in Table 1, depressed persons were older, more often women, less likely to be a (former) smoker or heavy alcohol drinker, and had more chronic diseases than the non-depressed. Although cortisol levels appeared to be somewhat higher in the depressed group, this was not statistically significant. The prevalence of metabolic syndrome and some of its components (abdominal obesity, low HDL cholesterol, antihypertensive medication) was higher among depressed participants. Use of corticosteroids (p = .59), antidepressants (p = .50), and benzodiazepines (p = .33) was not associated with metabolic syndrome (data not shown).

Table 2 shows that after adjustment for covariates there was a significant association between the severity of depressive symptoms (continuous CES-D score) and metabolic syndrome (OR per SD increase = 1.20, 95% CI = 1.02-1.41). However, the association between depressed mood (CES-D ≥ 20) and the metabolic syndrome was not statistically significant (OR = 1.30, 95% CI = 0.88-1.90). Level of urinary cortisol showed a significant linear association with metabolic syndrome (OR per SD increase = 1.18, 95% CI = 1.01-

Table 1. Baseline characteristics according to depressed mood

Characteristic	***Non-depressed*** *N = 688*	***Depressed*** *N = 179*	p [a]
Age (years), mean (SD)	73.7 (6.6)	75.8 (6.3)	<.001
Women, %	50.1	73.7	<.001
Years of education, mean (SD)	5.6 (3.1)	5.1 (3.5)	.12
Smoking status			
Nonsmoker, %	53.8	72.6	<.001
Former smoker, %	31.1	16.2	
Current smoker, %	15.1	11.2	
Alcohol intake (≥ 3 drinks a day), %	11.9	5.0	.007
Number of chronic diseases, mean (SD)	1.0 (0.9)	1.3 (1.0)	<.001
Severe renal function impairment, %	1.6	1.7	.94
Corticosteroid use, %	1.6	2.8	.29
Antidepressant use, %	1.7	10.6	<.001
Benzodiazepine use, %	15.0	36.3	<.001
Urine volume (ml), mean (SD)	1522 (551)	1521 (619)	.99
Baseline cardiovascular disease, %	13.1	11.2	.49
Baseline diabetes, %	12.4	10.6	.52
Cortisol			
Urinary cortisol (µg), mean (SD)	97.3 (43.2)	104.6 (63.5)	.15
Metabolic Syndrome			
Waist circumference (cm), mean (SD)	92.9 (10.0)	92.0 (11.6)	.36
Abdominal obesity, %	38.1	48.3	.01
Triglycerides (mg/dl), mean (SD)	128.7 (73.3)	128.8 (66.3)	.99
High triglycerides, %	24.9	25.1	.94
HDL cholesterol (mg/dl), mean (SD)	56.0 (15.3)	56.2 (14.7)	.92
Low HDL cholesterol, %	20.1	27.9	.02
Systolic blood pressure (mmHg), mean (SD)	150 (19.5)	150 (19.2)	.81
Diastolic blood pressure (mmHg), mean (SD)	84 (8.5)	84 (8.6)	.66
Antihypertensive medication, %	40.0	50.3	.01
High blood pressure, %	65.5	67.8	.56
Fasting glucose (mg/dl), mean (SD)	96.7 (25.8)	92.9 (23.4)	.08
Anti-diabetic medication, %	6.7	6.7	.99
High fasting glucose, %	16.9	12.8	.19
Metabolic syndrome, %	22.8	30.7	.03
Number of metabolic components, mean (SD)	1.7 (1.2)	1.8 (1.2)	.12

HDL = high-density lipoprotein. [a] Based on X^2 tests for dichotomous variables and independent t tests for continuous variables.

Table 2. Associations between depressed mood, urinary cortisol and metabolic syndrome

	Unadjusted [a]			Adjusted [b]			Adjusted for cortisol [c]		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Total sample *(N = 867)*									
Depressive symptoms [d]	1.29	1.11-1.50	.001	1.20	1.02-1.41	.03	1.11	0.94-1.32	.23
Depressed mood (CESD ≥ 20)	1.50	1.04-2.16	.03	1.30	0.88-1.90	.19	1.13	0.76-1.68	.55
Urinary cortisol [e]	1.12	0.96-1.30	.14	1.18	1.01-1.38	.04			
Depressed mood * urinary cortisol			.001			.003			
Non-depressed *(N = 688)*									
Urinary cortisol [d]	0.87	0.72-1.09	.25	0.95	0.67-1.18	.61			
Depressed *(N = 179)*									
Urinary cortisol [e]	1.52	1.18-1.94	.001	1.56	1.20-2.04	.001			

[a] Based on unadjusted logistic regression analyses; [b] adjusted for age, sex, education, smoking status, alcohol intake, number of chronic diseases, severe renal function impairment, and urine volume (analyses with cortisol only); [c] additionally adjusted for cortisol and cortisol^2; [d] per SD (= 8.7) increase in CES-D score; [e] per SD (= 48) increase in urinary cortisol (µg).

1.38). Additional adjustment for urinary cortisol and the squared term of urinary cortisol weakened the associations between depression and metabolic syndrome considerably: OR per SD increase in CES-D score became 1.11 (95% CI = 0.94-1.32) and the OR for depressed mood became 1.13 (95% CI = 0.76-1.68).

Figure 1 shows that the unadjusted prevalence of metabolic syndrome differed significantly (p = .008) across depressed mood and urinary cortisol tertile groups. Metabolic syndrome was more prevalent among the depressed in the highest cortisol tertile than in all other groups defined by tertile of cortisol and depression status. After adjustment, when persons had both depressed mood and urinary cortisol excretion in the highest tertile, the odds of metabolic syndrome was 1.84 (95% CI = 1.02-3.34, p = .04) times increased compared to persons without depression in the lowest tertile of urinary cortisol (reference group). Other depression/cortisol groups did not differ from the reference group (all p > .15). The interaction between depressed mood and urinary cortisol levels in predicting the odds of metabolic syndrome was significant (p interaction = .003). Consequently, additional analyses stratified for depressed mood were conducted. For those without depressed mood (N = 688), urinary cortisol was not associated with the metabolic syndrome (OR per SD increase = 0.95, 95% CI = 0.67-1.18). In the depressed group (N = 179), however, the odds of having the metabolic syndrome increased significantly with increasing levels of urinary cortisol (OR per SD increase = 1.56, 95% CI = 1.20-2.04).

Next, logistic regression analyses were repeated including sex by depressed mood, sex by urinary cortisol, and sex by depressed mood by urinary cortisol interaction terms, respectively. No significant sex interactions were found (all p > .15; data not shown). Also, when testing for CVD/diabetes interactions with depressed mood, urinary cortisol and their

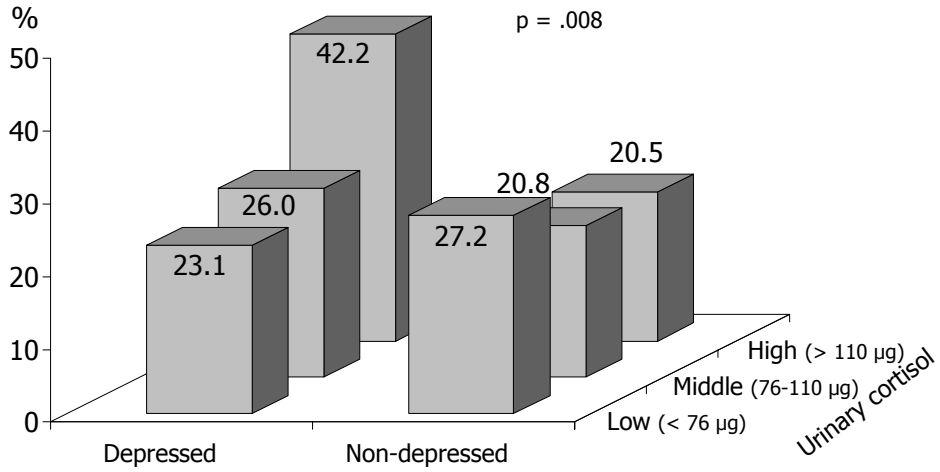

Figure 1. Prevalence of metabolic syndrome across depression status and tertiles of urinary cortisol

interacting effect, no significant interactions in the odds of having the metabolic syndrome were found (all $p > .15$; data not shown), which suggests that the link between depression, cortisol and metabolic syndrome is consistent for persons with and without CVD or diabetes.

Finally, Table 3 shows that depressive symptoms tended to be associated with waist circumference ($\beta = .064$, $p = .07$) and were negatively associated with HDL cholesterol levels ($\beta = -.070$, $p = .05$). However, no associations between depressed mood (CES-D ≥ 20) and any of the individual metabolic syndrome components were observed. Further, urinary cortisol levels showed a significant association with waist circumference ($\beta = .081$, $p = .02$) and fasting glucose levels ($\beta = .082$, $p = .02$). Moreover, there was a significant interaction between depressed mood and urinary cortisol levels in predicting levels of triglycerides ($p < .001$), HDL cholesterol ($p = .02$), and fasting glucose ($p = .003$), and a trend for an interaction for waist circumference ($p = .08$). Large waist circumference, high triglycerides levels and low HDL levels were significantly associated with higher cortisol levels in the depressed group only ($\beta = .178$, $p = .02$; $\beta = .247$, $p = .001$; $\beta = -.156$, $p = .04$, respectively). In the non-depressed group, higher levels of urinary cortisol were associated with lower triglycerides levels ($\beta = -.103$, $p = .01$) and with higher levels of fasting glucose ($\beta = .156$, $p < .001$).

Discussion

This community-based study among a large sample of older adults examined the relationship between depression, urinary cortisol and the metabolic syndrome. Higher levels of depressive symptoms were significantly associated with an increased prevalence of the

Table 3. Adjusted [a] associations between depressed mood, urinary cortisol, and continuous metabolic syndrome measures

	Waist circumference		***Triglycerides*** [b]		***HDL cholesterol*** [b]	
	β	p	β	p	β	p
Total Sample *(N = 867)*						
Depressive symptoms	.064	.07	.006	.88	-.070	.05
Depressed mood (CESD ≥ 20)	.025	.46	.009	.79	-.048	.15
Urinary cortisol	.081	.02	-.003	.92	-.017	.61
Depressed mood * urinary cortisol		.08		<.001		.02
Non-depressed *(N = 688)*						
Urinary cortisol	.028	.46	-.103	.01	.051	.17
Depressed *(N = 179)*						
Urinary cortisol	.178	.02	.247	.001	-.156	.04
	Systolic blood pressure		***Diastolic blood pressure***		***Fasting glucose*** [b]	
	β	p	β	p	β	p
Total Sample *(N = 867)*						
Depressive symptoms	-.049	.17	.024	.52	-.038	.30
Depressed mood (CESD ≥ 20)	-.033	.35	.024	.51	-.053	.13
Urinary cortisol	.014	.70	.025	.47	.082	.02
Depressed mood * urinary cortisol		.72		.58		.003
Non-depressed *(N = 688)*						
Urinary cortisol	.006	.87	.011	.78	.156	<.001
Depressed *(N = 179)*						
Urinary cortisol	.048	.53	.059	.46	-.065	.39

HDL = high-density lipoprotein. [a] Based on linear regression analyses adjusted for age, sex, education, smoking status, alcohol intake, number of chronic diseases, severe renal function impairment, and urine volume (analyses with cortisol only); [b] log-transformed values of triglycerides, HDL cholesterol and fasting glucose were used.

metabolic syndrome. This relationship might be partially mediated by urinary cortisol levels, since entering cortisol levels in the analyses reduced the association between depressive symptoms and metabolic syndrome. Moreover, we found an interaction between depressed mood and urinary cortisol in predicting metabolic syndrome. Among non-depressed participants, no association between urinary cortisol and metabolic syndrome was found. However, among depressed persons, urinary cortisol level did strongly predict the likelihood of having the metabolic syndrome. Persons with depressed mood and urinary cortisol levels in the highest tertile in particular had an increased prevalence of metabolic syndrome, which

suggests that hypercortisolemic depression constitutes a specific risk factor for the metabolic syndrome.

Our results are consistent with a few other studies that investigated the relationship between depressive symptoms and the metabolic syndrome. McCaffery et al.[27] found an association between depressive symptoms and metabolic risk in adult male twins, and Räikkönen et al.[28] confirmed this association in middle-aged women. Furthermore, a study by Kinder et al.[29] suggests that a history of depression increases the risk of metabolic syndrome in young women, but not men. Our results show that the relationship between depression and the metabolic syndrome extends to an older population. In addition, the involvement of the HPA-axis in the link between depression and the metabolic syndrome has been hypothesized by others[11], but no study has tested this directly. Our study provides evidence for the proposition that elevated cortisol levels increase the risk of the metabolic syndrome. An association between urinary cortisol and metabolic parameters was not observed in a study by Otte et al.[30]; however this study did not investigate the metabolic syndrome as a whole and did not examine depression by cortisol interactions. Most importantly, our study confirmed the hypothesis that when both depression and high cortisol levels are present, the odds of the metabolic syndrome is increased. This is consistent with a study by Weber-Hamann et al.[10], who found among 45 older women that hypercortisolemic depression was associated with increased visceral fat and a larger accumulation of visceral fat over time.[31]

How can it be explained that hypercortisolemic depression in particular is associated with a higher prevalence of metabolic syndrome? Previous findings from this and other aging studies have suggested that late-life depression may be associated with high as well as low levels of cortisol.[25,32,33] A number of studies provided some evidence that hypocortisolemic depression is associated with physical frailty and conditions characterized by fatigue and pain,[25,34,35] whereas hypercortisolemic depression is linked with more severe symptoms of depression.[25,36] In addition, it has been suggested that melancholic depression is associated with a hyperactive HPA-axis, whereas a hypoactive HPA-axis may be linked with atypical depression.[37] Therefore, it is possible that hyperactivity of the HPA-axis identifies a specific subtype of depression and it may be that only this subtype of depression is associated with the metabolic syndrome. What mechanisms, then, could underlie this association between hypercortisolemic depression and the metabolic syndrome? As described in a review by Björntorp,[38] cortisol binds to glucocorticoid receptors which have a high density in visceral fat depots; there it activates lipoprotein lipase and inhibits lipid mobilization, which leads to an accumulation of triglycerides in this area. This review also suggests that these effects are even more pronounced when combined with inhibition of sex steroids. Since low sex steroid hormones levels have also been associated with depression[39] this could explain why especially the combination of depression and high levels of cortisol increase the prevalence of the metabolic syndrome. Additionally, both depression and hyperactivity of the HPA-axis have been associated with increased inflammation,[40,41] which in turn have been linked to metabolic abnormalities.[42] Therefore, a combination of depression and hypercortisolemia could increase the risk for metabolic syndrome even more. Future studies should test these hypothesized explanations.

We evaluated whether depression and cortisol associations were consistent across the various metabolic syndrome components. Higher depressive symptoms were associated with larger waist circumference and lower HDL cholesterol levels, but for the other metabolic syndrome components no significant associations with depression were observed. Furthermore, in the depressed, we observed expected relationships between urinary cortisol and waist circumference, triglycerides and HDL cholesterol. This may indicate that hypercortisolemic depression is especially associated with the obesity-related components of the metabolic syndrome. However, Kopf et al.[43] found that in depressed persons higher cortisol levels were associated with a better lipid profile, although only in overweight subjects. In contradiction to some studies,[10,31,43] we did not find an association between hypercortisolemic depression and fasting glucose. In contrast, we found an association between cortisol levels and high fasting glucose in the non-depressed only. We do not have a clear explanation for this finding and it may be a chance finding, since it is contrary to findings for the other metabolic syndrome components. Lastly, no associations were found between depression/cortisol and high blood pressure, which may be in line with other research showing that the blood pressure component contributes less strongly and consistently to the concept of 'metabolic syndrome' compared to other components.[44]

Our definition of the metabolic syndrome did not exclude persons who already had CVD or diabetes. In fact, in our sample 19.7% and 31.2% of those with metabolic syndrome had CVD and diabetes. Since previous studies reported a relationship between depression and CVD or diabetes,[1-3] it is possible that an observed link between depression and metabolic syndrome merely reflects the association between depression and existing CVD/diabetes. However, we observed no CVD/diabetes interactions, suggesting that the relationship between depression and the metabolic syndrome is independent of the presence of CVD/diabetes and also exists among persons without CVD or diabetes.

Some limitations of our study should be acknowledged. Because of the cross-sectional nature of our study, we cannot make inferences about causality. Longitudinal analyses are needed to address this issue. Further, we did not have access to psychiatric diagnoses of depression. However, the CES-D is a commonly-used scale to measure depressive symptoms and has been linked to CVD outcomes. When persons have psychiatric diagnoses of depression, the association with the metabolic syndrome could even be stronger. Lastly, the InCHIANTI sample is comprised only of Italian older adults, who generally score rather high on depressive symptoms questionnaires compared to northern European countries and the US, which may be due to cultural but not per se clinical differences. Nevertheless, the Italian version of the CES-D has shown to be similarly predictive of major depression than other language versions, which suggests that its validity is comparable to that used in other international studies.[21] Strengths of our study were the large, randomly selected sample, and the 24-h urine measures of cortisol. This measure of cortisol is rather stable and insensitive to transient fluctuations in cortisol that lead to over- and underestimates in moment-by-moment sampling. On top, this assessment of the HPA-axis reflects biologically active, or unbound cortisol.

In conclusion, our results suggest a synergistic relationship between depression, cortisol, and the metabolic syndrome in an elderly population. Persons with

hypercortisolemic depression in particular may be at risk for having the metabolic syndrome, and therefore have an increased risk for developing cardiovascular disease or diabetes. Further research should confirm our findings and investigate the causality of the relationships between depression, cortisol and the metabolic syndrome using prospective studies.

Acknowledgements

This study was supported in part by grants R01 HL72972-01 (Dr. Penninx) and IRTA 2300 320 7 from the National Institutes of Health, Bethesda, MD (Drs. Suthers, Ble, & Schrager). The Extramural Branch of the NIH responsible for funding of the InCHIANTI study did not have any role in the design and conduct of the study, the collection, management, analysis and interpretation of the data nor the preparation, review or approval of the manuscript. Cortisol assays were supported by a professional services contract from the Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging.

References

1. Penninx BW, Guralnik JM, Mendes de Leon CF et al. Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age. *Am J Cardiol.* 1998;81:988-994.
2. Penninx BW, Beekman AT, Honig A et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry.* 2001;58:221-227.
3. Brown LC, Majumdar SR, Newman SC, Johnson JA. History of depression increases risk of type 2 diabetes in younger adults. *Diabetes Care.* 2005;28:1063-1067.
4. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. *JAMA.* 2006;295:2874-2881.
5. Vitaliano PP, Scanlan JM, Zhang J, Savage MV, Hirsch IB, Siegler IC. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosom Med.* 2002;64:418-435.
6. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation.* 2002;106:3143-3421.
7. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA.* 2002;287:356-359.
8. Raikkonen K, Keltikangas-Jarvinen L, Adlercreutz H, Hautanen A. Psychosocial stress and the insulin resistance syndrome. *Metabolism.* 1996;45:1533-1538.
9. Raikkonen K, Matthews KA, Kuller LH. Trajectory of psychological risk and incident hypertension in middle-aged women. *Hypertension.* 2001;38:798-802.
10. Weber-Hamann B, Hentschel F, Kniest A et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. *Psychosom Med.* 2002;64:274-277.
11. Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. *Psychoneuroendocrinology.* 2005;30:1-10.
12. Deuschle M, Weber B, Colla M, Depner M, Heuser I. Effects of major depression, aging and gender upon calculated diurnal free plasma cortisol concentrations: a re-evaluation study. *Stress.* 1998;2:281-287.
13. Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *J Affect Disord.* 2001;62:77-91.
14. Bjorntorp P, Rosmond R. Hypothalamic origin of the metabolic syndrome X. *Ann N Y Acad Sci.* 1999;892:297-307.
15. Ferrucci L, Bandinelli S, Benvenuti E et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc.* 2000;48:1618-1625.
16. Ferrucci L, Guralnik JM, Pahor M et al. Apolipoprotein E epsilon 2 allele and risk of stroke in the older population. *Stroke.* 1997;28:2410-2416.

17. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 1991;265:3255-3264.
18. Tannen RL, Weiner MG, Marcus SM. Simulation of the Syst-Eur randomized control trial using a primary care electronic medical record was feasible. *J Clin Epidemiol.* 2006;59:254-264.
19. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.
20. Beekman AT, Deeg DJ, van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med.* 1997;27:231-235.
21. Fava GA. Assessing depressive symptoms across cultures: Italian validation of the CES-D self-rating scale. *J Clin Psychol.* 1983;39:249-251.
22. Penninx BW, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJ, Wallace RB. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA.* 1998;279:1720-1726.
23. Penninx BW, Guralnik JM, Pahor M et al. Chronically depressed mood and cancer risk in older persons. *J Natl Cancer Inst.* 1998;90:1888-1893.
24. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1-266.
25. Penninx BW, Beekman AT, Bandinelli S et al. Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamo-pituitary-adrenal axis. *Am J Geriatr Psychiatry.* 2007;15:522-529.
26. Penninx BW, Geerlings SW, Deeg DJ, van Eijk JT, van Tilburg W, Beekman AT. Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry.* 1999;56:889-895.
27. McCaffery JM, Niaura R, Todaro JF, Swan GE, Carmelli D. Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. *Psychosom Med.* 2003;65:490-497.
28. Räikkönen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? *Metabolism.* 2002;51:1573-1577.
29. Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom Med.* 2004;66:316-322.
30. Otte C, Marmar CR, Pipkin SS, Moos R, Browner WS, Whooley MA. Depression and 24-hour urinary cortisol in medical outpatients with coronary heart disease: The Heart and Soul Study. *Biol Psychiatry.* 2004;56:241-247.
31. Weber-Hamann B, Werner M, Hentschel F et al. Metabolic changes in elderly patients with major depression: evidence for increased accumulation of visceral fat at follow-up. *Psychoneuroendocrinology.* 2006;31:347-354.
32. Morrison MF, Redei E, TenHave T et al. Dehydroepiandrosterone sulfate and psychiatric measures in a frail, elderly residential care population. *Biol Psychiatry.* 2000;47:144-150.
33. Oldehinkel AJ, van dB, Flentge F, Bouhuys AL, ter Horst GJ, Ormel J. Urinary free cortisol excretion in elderly persons with minor and major depression. *Psychiatry Res.* 2001;104:39-47.
34. Gur A, Cevik R, Nas K, Colpan L, Sarac S. Cortisol and hypothalamic-pituitary-gonadal axis hormones in follicular-phase women with fibromyalgia and chronic fatigue syndrome and effect of depressive symptoms on these hormones. *Arthritis Res Ther.* 2004;6:R232-R238.
35. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology.* 2005;30:1010-1016.
36. Nelson JC, Davis JM. DST studies in psychotic depression: a meta-analysis. *Am J Psychiatry.* 1997;154:1497-1503.
37. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry.* 2002;7:254-275.
38. Björntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev.* 2001;2:73-86.
39. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab.* 1999;84:573-577.
40. Sternberg EM, Chrousos GP, Wilder RL, Gold PW. The stress response and the regulation of inflammatory disease. *Ann Intern Med.* 1992;117:854-866.

41. Penninx BW, Kritchevsky SB, Yaffe K et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiatry.* 2003;54:566-572.
42. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol.* 1999;19:972-978.
43. Kopf D, Westphal S, Luley CW et al. Lipid metabolism and insulin resistance in depressed patients: significance of weight, hypercortisolism, and antidepressant treatment. *J Clin Psychopharmacol.* 2004;24:527-531.
44. Shen BJ, Todaro JF, Niaura R et al. Are metabolic risk factors one unified syndrome? Modeling the structure of the metabolic syndrome X. *Am J Epidemiol.* 2003;157:701-711.

Letter to the editor

Cortisol and insulin in depression and metabolic syndrome

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Psychoneuroendocrinology 2007; 32(7): 856

In their letter to the Editor, Castillo-Quan et al. suggest that hyperinsulinemia might be an underlying factor explaining the relationship between depression, hypercortisolemia, metabolic syndrome and diabetes. Although this is indeed a potentially interesting mechanism, our data do not provide much evidence for a large effect of hyperinsulinemia. In our study among 867 older persons,[1] we showed that hypercortisolemic depression was associated with the metabolic syndrome in an older population. Although we found a weak association between 24-h urinary cortisol and serum glucose in the total sample (adjusted $\beta = 0.08$, $p = .02$), among depressed persons ($N = 179$) cortisol appeared to be associated more strongly with the obesity-related components of the metabolic syndrome such as waist circumference, triglycerides, and high density lipoprotein cholesterol than with serum glucose. Actually, for the latter, the correlation with urinary cortisol was not found to be significant ($\beta = -0.07$, $p = .39$, see Table 3 in our paper).

In our study, we also had assessments of serum insulin available. When exploring the association between urinary cortisol levels and serum insulin, we found a significant but not very large association ($\beta = 0.07$, $p = .04$). However, as with glucose, the association between cortisol and insulin was not significant among the depressed ($\beta = 0.05$, $p = .48$). It seems therefore rather unlikely that in our conducted study insulin was the driving force behind the association between hypercortisolemic depression and the metabolic syndrome.

Acknowledgements

Partly supported by Grant R01 HL972972-01 from the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

References

1. Vogelzangs N, Suthers K, Ferrucci L et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology.* 2007;32:151-159.

Chapter 4

Late-life depression, cortisol and the metabolic syndrome

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American Journal of Geriatric Psychiatry 2009; 17(8): 716-721

Abstract

Objectives

High cortisol levels in depressed persons could possibly give rise to the metabolic syndrome. This study investigated cross-sectionally whether depression and high cortisol levels increased the odds of metabolic syndrome in an older community-based sample.

Methods

In 1212 participants, aged ≥ 65 years, enrolled in the Longitudinal Aging Study Amsterdam, depression (major [1-month diagnosis] or subthreshold [no 1-month diagnosis, but symptoms]), metabolic syndrome (modified Adult Treatment Panel III criteria) and free cortisol index (total serum cortisol / cortisol binding globulin) were assessed.

Results

Major depression was not associated with the metabolic syndrome (OR = 1.16, 95% CI = 0.54-2.49), but subthreshold depression was associated with a decreased odds (OR = 0.55, 95% CI = 0.37-0.82). Persons with higher levels of free cortisol index showed a higher odds of metabolic syndrome (OR per SD increase = 1.21, 95% CI = 1.06-1.39).

Conclusions

As persons with high cortisol levels more often had metabolic syndrome, hypercortisolemia within depressed persons may increase the risk of metabolic syndrome.

Introduction

Recently, several studies have linked metabolic syndrome, a clustering of cardiovascular risk factors including abdominal obesity, unfavorable lipid profile, high blood pressure and insulin resistance, with depression,[1-4] but results have been inconsistent.[5] Cortisol, an important product of the hypothalamic-pituitary-adrenal (HPA)-axis, has been associated with metabolic abnormalities, such as abdominal obesity and insulin resistance and is suggested to play a role in the association between depression and metabolic syndrome.[6] As depression has been associated with both hypo- and hypercortisolemia, at least in later life,[7,8] this may partly account for inconsistent findings in the association between depression and metabolic syndrome. Little research has addressed the joint effect of depression and cortisol on the metabolic syndrome in older persons. One recent study in older persons showed an increased likelihood of metabolic syndrome in hypercortisolemic depressed persons only, supportive of a mediating role of cortisol.[9] Identifying depression subgroups at increased risk of metabolic syndrome is important for treatment and prevention of (consequences of) depression. Furthermore, most studies assessed depression using symptoms scales, but distinguishing symptoms from a major depression diagnosis might be relevant. Therefore, we investigated the relationship of depression (symptoms or diagnosis) and cortisol with metabolic syndrome in community-dwelling older persons.

Methods

Study population

Data are from the Longitudinal Aging Study Amsterdam (LASA), a population-based older cohort (for details see[10]). In short, a random sample of men and women aged 55-85 years, stratified by age, sex, urbanization and expected five year mortality, was drawn from the population registries of eleven municipalities in three regions in the Netherlands. Respondents gave informed written consent and the study was approved by the Ethical Review Board of the VU University Medical Center. 3107 Respondents aged 55 years and over participated in the baseline examination (1992/1993) conducted at the respondents' homes. Data on metabolic syndrome were available at the first follow-up assessment (1995/1996; N = 2545, mainly lost to mortality) for persons aged 65 or above (N = 1720). Persons with complete data on metabolic syndrome, depression and cortisol (N = 1212) were younger ($p < .001$), more often men ($p = .03$), higher educated ($p < .001$), and had less depressive symptoms ($p = .004$) than persons not included in the analytic sample (N = 508).

Depression

The Center for Epidemiologic Studies-Depression Scale (CES-D), a 20-item self-report scale on depressive symptoms in the past week, was administered (in our study: Cronbach alpha = 0.87). Participants scoring ≥ 16, a commonly used cut-off score indicating clinically relevant depressive symptoms,[11] were administered the Diagnostic Interview Schedule to assess major depression disorder in the past month according to DSM-III criteria. Subthreshold depression was defined as a CES-D score ≥ 16, but no major depression in the past month.

Cortisol

Blood samples were collected in the morning. Total serum levels of cortisol were determined using a commercially available competitive immunoassay (ACS:Centauer, Bayer Diagnostics, The Netherlands). Cortisol binding globulin (CBG) levels were determined using a radio immunoassay (Medgenix Diagnostics, Belgium). Bound to CBG, cortisol is biologically inactive. Therefore, a free cortisol index was computed as total serum cortisol / CBG.

Metabolic syndrome

Blood pressure was measured in sitting position using a standard mercury sphygmomanometer. Waist circumference was averaged over two readings measured midway between the lower rib margin and the iliac crest. Fructosamine was determined by a colorimetric test, and high-density lipoprotein (HDL) cholesterol and triglycerides by an enzymatic colorimetric test (Roche diagnostics, Mannheim, Germany). Prescription drugs taken in the previous two weeks were identified by container inspection.

Metabolic syndrome was defined by slightly modified National Cholesterol Education Program Adult Treatment Panel III[12] criteria as presence of three or more of the following: (i) waist circumference > 102 cm in men or > 88 cm in women; (ii) triglyceride level ≥ 1.7 mmol/l; (iii) HDL cholesterol < 1.0 mmol/l in men or < 1.3 mmol/l in women; (iv) blood pressure ≥ 160/90 mmHg or anti-hypertensive medication; (v) fructosamine ≥ 247 umol/l or anti-diabetic medication. Considering the older age of the study population, the cut-off for blood pressure was increased (original criterion: ≥ 130/85 mmHg). Because the instructions before blood sampling allowed respondents to take tea and dry toast but no diary products, fasting blood samples could not be fully guaranteed. Therfore, fructosamine, which is less affected by eating, was used as a proxy for glucose. The cutoff of 247 umol/l for fructosamine corresponds to the cut-off of 6.1 mmol/l for fasting plasma glucose in terms of sensitivity and specificity for insulin resistance.[13]

Metabolic syndrome components were analyzed continuously. For persons using antihypertensive medication 10 and 5 mmHg were added to systolic and diastolic blood pressure, respectively, and persons on anti-diabetics were at least given a value of 247 umol/l for fructosamine, as in a previous study.[9] To normalize distributions, triglycerides, HDL cholesterol and fructosamine were log-transformed.

Covariates

Covariates were selected a priori and included sociodemographic (age, sex, and educational level [low, medium, high]), and lifestyle variables (smoking status [non, former, current], current alcohol intake [yes/no excessive drinking], and physical activity [total day activities in min/day]). Cardiovascular disease (myocardial infarction, angina pectoris, stroke) was assessed combining self-reports, medication use, and general practitioner records in a standardized algorithm. Diabetes and other chronic diseases (including lung disease, arthritis, and cancer) were self-reported.

Statistical analyses

Adjusted logistic and linear regression analyses assessed associations between depression or cortisol with (number of) metabolic syndrome (components) as outcome. To assess whether hypercortisolemia contributed to metabolic syndrome in both depressed and non-depressed, a cortisol by depression status interaction was tested.

Results

Mean age of the 1212 participants was 75.3 years (SD = 6.5), 51.5% were women, and 40.9% had low education. Of the participants, 12.5% had a subthreshold depression, 2.6% had a major depression in the past month, and 36.4% had metabolic syndrome. Mean free cortisol index level was 12.4 (SD = 4.6). Sample characteristics according to depression status are reported elsewhere.[7] Table 1 shows adjusted regression analyses with metabolic syndrome (components) as outcome. Compared to no depression, subthreshold depression decreased odds of metabolic syndrome (OR = 0.55, 95% CI = 0.37-0.82), while major depression did not change probability of metabolic syndrome (OR = 1.16, 95% CI = 0.54-2.49). High free cortisol index increased likelihood of metabolic syndrome (OR per SD increase = 1.21, 95% CI = 1.06-1.39). There was no significant free cortisol index by depression status interaction (subthreshold depression: p = .85; major depression p = .18), indicating that cortisol is associated with metabolic syndrome in both non-depressed and depressed subjects. Similar associations for depression and cortisol were found using number of metabolic syndrome components as outcome (not shown). Overall, associations between depression and individual metabolic syndrome components were in the same direction as with metabolic syndrome (see Table 1). Significant associations of free cortisol index were found with higher triglyceride levels (β = .080), lower HDL cholesterol levels (β = -.153), and higher systolic blood pressure (β = .067).

Conclusions

This population-based study among older persons showed that persons with high levels of cortisol have an increased probability of metabolic syndrome. No associations between major depression and metabolic syndrome were found. Unexpectedly, subthreshold depression decreased the odds of metabolic syndrome. Up until now some studies did show a positive association between depression or depressive symptoms and metabolic syndrome,[1-4] but absence of associations have been reported too.[5] One recent study by Skilton et al.,[3] reporting an increased depression rate in metabolic syndrome, was conducted among a population at risk for cardiovascular disease. Other studies that related depression to the metabolic syndrome were conducted among young adults[1] or in middle-aged populations.[2,4,14] One study in the older general population reported only a weak association between depressive symptoms and metabolic syndrome in White persons only.[15] Also, Giltay et al.[16] showed in an older general population, that persons who scored high on 'classic' cardiovascular risk factors related to the metabolic syndrome, such as obesity, hypertension, hypercholesterolemia and diabetes did not report more depressive symptoms than persons who scored low on these risk factors. Possibly, in a more diffuse general older population, associations are not as clear. As was recently also pointed out by Lyness,[17]

Table 1. Depression, free cortisol index and association with metabolic syndrome [a] (components [b])

N = 1212		***Metabolic syndrome***			***Waist circumference***		***Triglycerides*** [d]	
	N	OR	95%CI	p	β	p	β	p
Depression								
Depressive symptoms [c]	1212	0.85	0.74-0.97	.02	-.063	.03	-.039	.20
Depression status								
No depression	1029	Ref			Ref		Ref	
Subthreshold depression	152	0.55	0.37-0.82	.004	-.085	.002	-.032	.27
Major depression	31	1.16	0.54-2.49	.71	.024	.38	-.007	.81
Cortisol								
Free cortisol index [c]	1212	1.21	1.06-1.39	.004	-.040	.18	.080	.01
Free cortisol tertiles								
Low free cortisol index (< 9.9)	404	Ref			Ref		Ref	
Middle free cortisol index (9.9-14.1)	404	1.09	0.79-1.49	.61	-.009	.78	.048	.16
High free cortisol index (> 14.1)	404	1.44	1.04-1.99	.03	-.030	.37	.056	.11

		HDL cholesterol [d]		***Systolic bl. Pressure***		***Diastolic bl. pressure***		***Fructo-samine*** [d]	
	N	β	p	β	P	β	p	β	p
Depression									
Depressive symptoms [c]	1212	.089	.003	-.044	.16	.053	.09	-.026	.33
Depression status									
No depression	1029	Ref		Ref		Ref		Ref	
Subthreshold depression	152	.074	.009	-.037	.22	.042	.16	-.033	.19
Major depression	31	-.011	.68	-.018	.53	.009	.77	-.021	.41
Cortisol									
Free cortisol index [c]	1212	-.153	<.001	.067	.03	.046	.14	.043	.10
Free cortisol tertiles									
Low free cortisol index (< 9.9)	404	Ref		Ref		Ref		Ref	
Middle free cortisol index (9.9-14.1)	404	-.073	.03	.056	.11	.036	.30	.002	.95
High free cortisol index (> 14.1)	404	-.155	<.001	.047	.19	.018	.62	.045	.14

HDL: high-density-lipoprotein. [a] Based on logistic and [b] linear regression analyses adjusted for age, sex, educational level, smoking status, alcohol intake, physical activity, diabetes, cardiovascular disease, and number of other chronic diseases; [c] OR per SD increase: depressive symptoms SD = 7.6; free cortisol index SD = 4.6; [d] to normalize distributions, triglycerides, HDL cholesterol and fructosamine were log-transformed.

associations between depression and disease might be more specific in less heterogeneous subpopulations.

A previous LASA paper[7] showed that older depressed persons either had low or high levels of cortisol, with the majority of depressed persons in this study having low cortisol. It is possible that the nonlinear association between depression and cortisol precluded us from finding a positive association between depression and metabolic syndrome, which we hypothesized to be partly mediated by cortisol. Contrary to our expectations, persons with subthreshold depression were less likely to have metabolic syndrome. As cortisol levels did correlate with metabolic syndrome, it is possible that the large proportion of depressed persons with low cortisol levels in fact decreased their odds of metabolic syndrome. Low cortisol levels in older persons may reflect biological exhaustion or frailty and has been associated with reversed metabolic abnormalities.[18] In contrast, increased HPA-axis activity stimulates accumulation of triglycerides in visceral regions[6] and therefore increases the risk of metabolic syndrome. Another recent study, in which hypo- and hypercortisolemia was more evenly spread over depressed persons,[8] did show that hypercortisolemic depression was associated with metabolic syndrome in older persons.[9] Together, these results suggest that hypercortisolemia within depressed persons may increase the risk of metabolic syndrome. Longitudinal studies should address the relative timing of disturbed HPA-axis activity, depression and metabolic syndrome.

Associations for cortisol were relatively consistent across metabolic syndrome components, with strongest associations for HDL cholesterol, triglycerides and systolic blood pressure. In the general population and among depressed persons, associations of cortisol with HDL cholesterol and triglycerides have been reported before. In contrast with our findings, these studies also found an association of cortisol with abdominal obesity.[9,19]

Some limitations of our study need to be addressed. As fasting blood levels could not be fully guaranteed, this might have affected our findings for triglycerides, and to a lesser extent HDL cholesterol. However, a recent study found that lipid profiles at most change minimally in response to normal food and non-fasting levels still predict cardiovascular events.[20] Yet, would truly fasting lipid levels have been used in our study, associations of cortisol with triglycerides and HDL cholesterol might have been even stronger. Furthermore, fructosamine was used as a proxy of glucose, because it is less affected by eating. The cutoff for fructosamine we used was shown to have maximal effectiveness in discriminating subjects with impaired glucose tolerance from subjects with normal glucose tolerance.[13] However, it is possible that, unlike fructosamine, glucose levels would have shown associations with depression or cortisol.

Our study was one of the very few using psychiatric diagnoses of major depression,[1] in stead of a depression symptoms scale only[2-5,14,15] and suggests that associations between depression and metabolic syndrome might be different for persons with depressive symptoms compared to persons with a depression diagnosis. This might indicate partly different constructs, although the number of major depression cases in our study was relatively small. Therefore, no definite conclusions can be drawn from our study on the association between major depression and the metabolic syndrome.

In this study, depression, either defined by diagnosis or symptom scale, was not associated with an increased odds of metabolic syndrome. However, high cortisol levels did increase the likelihood of metabolic syndrome. This suggests that when depression presents with hypercortisolemia it might be important to be watchful of metabolic syndrome to be able to prevent metabolic and cardiovascular health consequences.

Acknowledgements

The Longitudinal Aging Study Amsterdam (LASA) is funded by the Dutch Ministry of Health, Welfare and Sports. Data analyses were supported by grant R01-HL72972-01 from the National Heart, Lung, and Blood Institute (NHLBI).

References

1. Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom Med.* 2004;66:316-322.
2. Raikkonen K, Matthews KA, Kuller LH. Depressive symptoms and stressful life events predict metabolic syndrome among middle-aged women: a comparison of World Health Organization, Adult Treatment Panel III, and International Diabetes Foundation definitions. *Diabetes Care.* 2007;30:872-877.
3. Skilton MR, Moulin P, Terra JL, Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. *Biol Psychiatry.* 2007;62:1251-1257.
4. Vanhala M, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Koponen H. Depressive symptoms predispose females to metabolic syndrome: a 7-year follow-up study. *Acta Psychiatr Scand.* 2009;119:137-142.
5. Herva A, Rasanen P, Miettunen J et al. Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. *Psychosom Med.* 2006;68:213-216.
6. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev.* 2001;2:73-86.
7. Bremmer MA, Deeg DJ, Beekman AT, Penninx BW, Lips P, Hoogendijk WJ. Major depression in late life is associated with both hypo- and hypercortisolemia. *Biol Psychiatry.* 2007;62:479-486.
8. Penninx BW, Beekman AT, Bandinelli S et al. Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamo-pituitary-adrenal axis. *Am J Geriatr Psychiatry.* 2007;15:522-529.
9. Vogelzangs N, Suthers K, Ferrucci L et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology.* 2007;32:151-159.
10. Deeg DJ, van Tilburg T, Smit JH, de Leeuw ED. Attrition in the Longitudinal Aging Study Amsterdam. The effect of differential inclusion in side studies. *J Clin Epidemiol.* 2002;55:319-328.
11. Beekman AT, Deeg DJ, van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med.* 1997;27:231-235.
12. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation.* 2002;106:3143-3421.
13. Herdzik E, Safranow K, Ciechanowski K. Diagnostic value of fasting capillary glucose, fructosamine and glycosylated haemoglobin in detecting diabetes and other glucose tolerance abnormalities compared to oral glucose tolerance test. *Acta Diabetol.* 2002;39:15-22.

14. Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Vanhala M. Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry.* 2008;69:178-182.
15. Vogelzangs N, Beekman AT, Kritchevsky SB et al. Psychosocial risk factors and the metabolic syndrome in elderly persons: findings from the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci.* 2007;62:563-569.
16. Giltay EJ, Zitman FG, Kromhout D. Cardiovascular risk profile and subsequent disability and mental well-being: the Zutphen Elderly Study. *Am J Geriatr Psychiatry.* 2008;16:874-882.
17. Lyness JM. Depression and comorbidity: objects in the mirror are more complex than they appear. *Am J Geriatr Psychiatry.* 2008;16:181-185.
18. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology.* 2005;30:1010-1016.
19. Weber-Hamann B, Hentschel F, Kniest A et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. *Psychosom Med.* 2002;64:274-277.
20. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. *Circulation.* 2008;118:2047-2056.

Chapter 5

Depressive symptoms and change in abdominal obesity in older persons

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Archives of General Psychiatry 2008; 65(12): 1386-1393

Abstract

Context
Depression has been hypothesized to result in abdominal obesity through the accumulation of visceral fat. No large study has tested this hypothesis longitudinally.

Objective
To examine whether depressive symptoms predict an increase in abdominal obesity in a large population-based sample of well-functioning older persons.

Design
The Health, Aging, and Body Composition Study, an ongoing prospective cohort study with 5 years of follow-up.

Setting
Community-dwelling older persons residing in the areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee.

Participants
A total of 2088 well-functioning white and black persons aged 70 to 79 years.

Main Outcome Measures
Baseline depression was defined as a Center for Epidemiologic Studies Depression score of 16 or higher. At baseline and after 5 years, overall obesity measures included body mass index (calculated as weight in kilograms divided by height in meters squared) and percent body fat (measured by dual-energy x-ray absorptiometry). Abdominal obesity measures included waist circumference, sagittal diameter, and visceral fat (measured by computed tomography).

Results
After adjustment for sociodemographics, lifestyle, diseases and overall obesity, baseline depression was associated with a 5-year increase in sagittal diameter ($\beta = .054$, $p = .01$) and visceral fat ($\beta = .080$, $p = .001$).

Conclusions
This study shows that depressive symptoms result in an increase in abdominal obesity independent of overall obesity, suggesting that there may be specific pathophysiological mechanisms that link depression with visceral fat accumulation. These results might also help explain why depression increases the risk of diabetes and cardiovascular disease.

Introduction

Depression is common in later life. Clinically relevant depressive symptoms are present in 10% to 15% of the older population.[1] According to the World Health Organization, depression is among the leading disorders causing disability and will be the second most important cause of disability worldwide in 2020.[2] Depression has been associated with the onset of diabetes, cardiovascular disease (CVD) and cardiac mortality.[3-6] To better prevent occurrence of these major disabling and life-threatening diseases, more insight into underlying mechanisms relating depression to these disorders, is needed.

Neuroendocrine disturbances found in depressed persons include dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis and hypothalamic-pituitary-gonadal axis, indicated by high levels of cortisol[7,8] and low levels of sex steroid hormones,[9] respectively. In addition, high levels of inflammatory markers have been observed in persons who report clinically relevant depressive symptoms.[10] Similar abnormalities have been identified in persons with abdominal obesity.[11,12] Consequently, Björntorp hypothesized that chronic stress and/or depression results in abdominal obesity through long-term activation of the HPA-axis.[13] Björntorp argued that elevated cortisol, particularly when combined with low sex steroid hormones, causes fat to accumulate in visceral adipose tissue. This might be due to specific properties of visceral fat, such as a high density of glucocorticoid receptors.[14] Excess visceral fat, as indicated by abdominal obesity, subsequently has been found to predict diabetes, CVD, and mortality to a greater degree than overall obesity.[15-18]

Until now, no large study has longitudinally tested the hypothesis that depressive symptoms lead to an increase in visceral fat. Some cross-sectional studies report an association between abdominal obesity and depression[19-24] independent of overall obesity. One prospective study found that 29 patients with major depression had a larger increase in visceral fat than 17 persons without depression.[25]

The present study investigates the longitudinal association between depressive symptoms at baseline and 5-year changes in abdominal obesity in a large community sample of older persons. We hypothesize that depressive symptoms at baseline will predict an increase in abdominal obesity over time and that this association is specific to abdominal obesity compared with overall obesity.

Methods

Study population

Data are from 3075 well-functioning white and black men and women aged 70 to 79 years enrolled in the Health, Aging, and Body Composition (Health ABC) study, an ongoing prospective cohort study. Participants were recruited in 1997 and 1998 from a sample of white and black Medicare-eligible beneficiaries residing in the areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Race was self-identified and black persons were over-sampled to be able to examine race differences. Subjects were eligible if they reported no difficulty with walking for a quarter of a mile, walking up 10 steps, or performing activities of daily living. Subjects were ineligible if they had severe difficulty communicating, had active cancer treatment in the past three years, had plans to move out of the area, or were participating in a randomized trial of a lifestyle intervention. All participants signed an

informed written consent form approved by the institutional review boards of the clinical sites. In the present study, persons with missing baseline data on depressive symptoms and/or obesity were excluded (N = 26). In addition, persons without obesity data at the 5-year assessment in 2002-2003 were excluded (N = 961; 375 persons had died, 13 were lost to follow-up, 63 did not participate that year, and 510 were assessed by phone interview only), leaving 2088 persons for the present analyses. Included persons (N = 2088) were younger (73.4 versus 74.1 years at baseline; $p < .001$), more often women (52.7% versus 48.9%; $p = .05$), white (63.6% versus 47.2%; $p < .001$), and college educated (46.7% versus 32.8%; $p < .001$) and had lower rates of depression at baseline (4.0% versus 6.2%; $p = .007$) than excluded persons (N = 987).

Depressive symptoms

During the baseline interview, depressive symptoms were measured with the 20-item Center for Epidemiologic Studies Depression (CES-D) scale assessing depressive symptoms in the previous week.[26] This scale, ranging from 0 to 60, has been widely used in older populations and has been shown to be a valid and reliable instrument among the elderly.[27] In our study the internal consistency was high: Cronbach alpha = 0.81. A score of 16 or higher, the usual cut-off, identified persons with clinically relevant depressive symptoms. Although this definition does not reflect a psychiatric diagnosis of depression, for convenience in this paper we will refer to this cut-off measure as *depression*. In addition, the CES-D 10 item version, which has shown good predictive accuracy when compared with the 20-item CES-D scale,[28] was administered at follow-up after 2, 3, 4, and 5 years. For sensitivity analyses, depressed persons were subdivided into persons who were only depressed at baseline (single depression) and those who also had depression at at least one follow-up assessment (CES-D-10 ≥ 10) (persistent or recurrent depression).

Obesity

All obesity measures were assessed at the clinic visit at baseline and after 5 years.

Overall obesity

Body weight was measured on a standard balance beam scale to the nearest 0.1 kg. Height was measured barefoot using a wall-mounted stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared. Total mass (grams) and total fat mass (grams) were determined via a whole body dual energy x-ray absorptiometry (DXA) scan using fan beam technology (QDR4500A; Hologic, Waltham, Massachusetts, US). The percent body fat was defined as (total fat mass / total mass) * 100; when total mass was missing, weight (grams) was used instead.

Abdominal obesity

Computed tomography (CT) scanning was performed at the level between the fourth and fifth lumbar vertebrae to measure visceral fat (cm^2) using a Somatom Plus 4 (Siemens, Erlangen, Germany) or a Picker PQ 2000S (Marconi Medical Systems, Cleveland, Ohio, US) scanner in Memphis and a 9800 Advantage scanner (General Electric, Milwaukee, Wisconsin,

US) in Pittsburgh. The scans were conducted at 120 kilovolt (peak) and 200 to 250 mA/s at a slice thickness of 10 mm. Areas were calculated by multiplying the number of pixels of a given tissue type by the pixel area using IDL development software (Research Systems Inc, Boulder, Colorado, US). Visceral fat was manually distinguished from abdominal subcutaneous fat by tracing along the fascial plane defining the internal abdominal wall. Quality of repositioning on CT scans between baseline and the 5-year assessment was rated, incorporating abdominal level and anatomical landmarks. In addition to the continuous measure of 5-year change in visceral fat, a categorical measure was constructed, defining loss, no change, or gain of visceral fat. A cut-off of 30% change in visceral fat was selected, because this approximated 1 SD in the visceral fat change score. Besides the direct CT measure of visceral fat, some anthropometric measures were assessed. Maximum sagittal diameter (cm), the distance between the abdomen and back, was derived from the CT scans. Waist circumference (cm) was measured at the largest abdominal circumference to the nearest 0.1 cm using a flexible plastic tape measure.

Baseline characteristics

Sociodemographic characteristics included age, sex, race (white, black), site (Pittsburgh, Memphis), and education (less than high school, high school, post-secondary education). We also assessed lifestyle characteristics known to be related to both abdominal obesity and depression: smoking status (nonsmoker, former, or current), current alcohol intake (0-1 versus ≥ 2 drinks per day) and physical activity (sum of weight training, high and medium intensity exercise, aerobic dance, [exercise] walking, and stair climbing [in kilocalories/week]). Presence of baseline diabetes and CVD (including stroke or transient ischemic attack, myocardial infarction, angina pectoris, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting) were adjudicated using standardized algorithms considering various sources of information: self-report, medication use, oral glucose tolerance testing, and medical claims data from the former Health Care Financing Administration. Number of other chronic diseases was mainly based on self-report and included congestive heart failure, peripheral arterial disease, cancer, lung disease, osteoarthritis, osteoporosis, gastrointestinal disease, prostate disease, thyroid disease, Parkinson's disease, and kidney disease. In addition, all medications regularly taken in the 2 weeks before baseline were recorded and coded according to the Iowa Drug Information System (IDIS).[29] From this inventory, the total number of prescription medications taken was calculated. In addition, use of antidepressant medication was ascertained, which included monoamine oxidase inhibitors (IDIS code 281605), tri/tetracyclic antidepressants (IDIS code 281606), selective serotonin reuptake inhibitors (IDIS code 281607), and other antidepressants (IDIS code 281604), regardless of reason. Other psychoactive medication included antipsychotic (phenothiazines, IDIS code 281609; butyrophenones, IDIS code 282610; other, IDIS code 281608) and anxiolytic (benzodiazepines, barbiturates, other, IDIS code 2824) medication.

Statistical analysis

Sample characteristics were compared between depressed and non-depressed persons using X^2 tests for dichotomous and categorical variables and independent t tests for continuous variables. Because some of the obesity measures differ greatly between men and women, sex-adjusted means were presented based on analyses of covariance. Paired-sample t-tests were performed to assess whether 5-year changes in obesity were statistically significant. To evaluate the association between depressive symptoms at baseline (both continuous as well as dichotomous) and 5-year change in abdominal obesity, linear regression analyses were conducted with abdominal obesity change scores as the outcome. For comparison, associations between depressive symptoms and overall obesity were also presented. Covariates were a priori selected and initial analyses were adjusted for the corresponding baseline obesity measure and sociodemographic variables (sex, age, race, site, and education). Next, to assess whether results were independent of baseline overall obesity, abdominal obesity analyses were additionally adjusted for BMI. Finally, because lifestyle, abdominal obesity-related diseases, and general health status might partly explain the association between abdominal obesity and depression, we examined their role by additionally adjusting analyses for smoking status, alcohol intake, physical activity, prevalent diabetes, prevalent CVD, number of other chronic diseases, and number of prescription medications taken.

Because depression has also been associated with weight loss,[30,31] it is possible that a U-shaped association exists between depression and change in visceral fat, with depression being associated with both gain and loss of visceral fat. Therefore, it was checked whether baseline depression was also associated with a decrease in visceral fat, distinct from a potential increase in visceral fat. For this purpose, an adjusted multinomial logistic regression analysis was performed using categories of visceral fat change (loss, no change, gain) as the outcome. By choosing the no change group as the reference category, this analysis gives 2 odds ratios, one assessing the risk of losing visceral fat when depressed at baseline, and one assessing the risk of gaining visceral fat when depressed at baseline. Furthermore, to verify that the association between depression and visceral fat was independent of change in BMI a linear regression analysis was performed with change in visceral fat as the outcome, adjusted for change in BMI. In addition, it was tested whether an interaction existed with change in BMI, to assess whether the relationship between depression and change in visceral fat was consistent across the whole range from weight loss and weight stability to weight gain.

Because sex differences in the relationships between depression, abdominal obesity, and CVD have been observed[3,18] and because fat distribution differs across sex and race, all analyses were repeated including sex by depression and sex-specific race by depression interaction terms, to test whether findings were consistent across sex and race. For graphing purposes, adjusted mean 5-year changes in abdominal obesity were calculated using analyses of covariance. Finally, because a significant proportion of persons enrolled at baseline did not have a clinic visit after 5 years, leaving the most healthy persons for analysis, missing values at follow-up were multiply imputed. Multiple imputation was established by Multivariate Imputation by Chained Equations[32] using R statistical software.

Obesity follow-up measures were only imputed if depression and the corresponding obesity measure at baseline were not missing. Missing follow-up obesity values were 5 times imputed by predictive mean matching using information from all available covariates (sex, age, race, site, education, smoking status, alcohol intake, physical activity, prevalent diabetes, prevalent CVD, number of other chronic diseases, number of prescription medications taken, antidepressant medication, other psychoactive medication), predictors (CES-D score, yes or no depression, yes or no persistent depression), the corresponding baseline obesity measure, BMI and change in BMI for abdominal obesity measures, and visceral fat and change in visceral fat for overall obesity measures. Fully adjusted (including adjustment for yes/no imputed value) linear regression analyses that associated depression with change in obesity were conducted on each of the 5 newly created datasets and the results were pooled.

Results

Sample characteristics

At baseline, the mean (SD) age of the participants was 73.4 (2.8) years, 52.7% were women, and 36.4% were black. Depression was present in 4.0% of participants and the mean (SD) BMI was 27.3 (4.7). Women had a greater percent body fat than men (40.5% versus 29.5%), but had less visceral fat (130.7 cm^2 versus 157.4 cm^2). Overall, 5-year changes in obesity were small, although some increases in obesity were seen in men while decreases in abdominal obesity were observed in women, especially in visceral fat (-11.4 cm^2), consistent with earlier reported findings in this older sample.[33] Visceral fat correlated more strongly with waist circumference (Pearson's r = 0.63) and sagittal diameter (Pearson's r = 0.75) than with BMI (Pearson's r = 0.54). Table 1 shows the sample characteristics for persons with and without depression. Persons with baseline depression were less educated, had more chronic diseases and were taking more prescription medication. Depressed persons had slightly higher sex-adjusted percent body fat at baseline (35.2% versus 36.6%, p = .02) and showed a (larger) sex-adjusted 5-year increase in sagittal diameter (0.2 cm versus 0.9 cm, p = .007) and visceral fat (-7.1 cm^2 versus 9.0 cm^2, p = .001) than non-depressed persons.

Baseline depressive symptoms and 5-year change in abdominal obesity

Table 2 describes the results of adjusted linear regression analyses assessing the association between baseline CES-D score (continuous) and depression (CES-D ≥ 16) with 5-year changes in obesity measures. No significant associations were found for the continuous CES-D score or the depression variable with 5-year changes in overall obesity (BMI or percent body fat). In contrast, after full adjustment for covariates, baseline depression was associated with increases in sagittal diameter (β = .054, p = .01), and visceral fat (β = .080, p = .001), with a trend for an increase in waist circumference (β = .031, p = .08). For the continuous CES-D score these associations were still consistent but somewhat attenuated (waist circumference: β = .026, p = .15; sagittal diameter: β = .037, p = .10; visceral fat: β = .042, p = .07).

Table 1. Sample characteristics

Characteristic	***CES-D < 16*** *N = 2004*	***CES-D ≥ 16*** *N = 84*	p [a]
Sociodemographic variables			
Age (years), mean (SD)	73.4 (2.8)	73.6 (2.9)	.50
Black, %	36.3	38.1	.74
Memphis site, %	50.0	42.9	.20
Education, %			
Less than high school	21.6	27.4	.05
High school	31.2	36.9	
Postsecondary	47.2	35.7	
Lifestyle variables			
Current smoker, %	7.7	11.9	.16
> 1 Alcoholic drink / day, %	7.3	7.1	.96
Physical activity (kcal/week), mean (SD)	1177 (2023)	1118 (2615)	.80
Somatic comorbidities			
Prevalent diabetes, %	20.9	17.9	.50
Prevalent cardiovascular disease, %	21.1	25.0	.39
Number of other chronic diseases, mean (SD)	1.2 (1.0)	1.5 (1.1)	.02
Number of prescription medications, mean (SD)	3.0 (2.4)	4.2 (3.4)	.002
Depression variables			
Baseline CES-D score (0-60), mean (SD)	3.8 (3.7)	20.9 (5.3)	<.001
Baseline antidepressant use, %	5.0	13.1	.001
Baseline other psychoactive medication use, %	6.3	22.6	<.001
Obesity variables			
Overall obesity			
Body mass index (kg/m^2), mean (SD)	27.3 (4.7)	27.9 (4.7)	.28
Percent body fat, mean (SD)	35.2 (5.2)	36.6 (5.2)	.02
5-y Change in body mass index, (kg/m^2), mean (SD)	-0.0 (1.8)	0.2 (2.2)	.18
5-y Change in percent body fat, mean (SD)	0.4 (2.7) [b]	0.3 (2.7)	.78
Abdominal obesity			
Waist circumference (cm), mean (SD)	99.3 (12.2)	100.7 (12.2)	.29
Sagittal diameter (cm), mean (SD)	23.5 (3.3)	23.5 (3.3)	.87
Visceral fat (cm^2), mean (SD)	142.8 (64.7)	155.7 (64.7)	.08
5-y Change in waist circumference (cm), mean (SD)	-0.8 (9.3) [b]	0.9 (9.3)	.09
5-y Change in sagittal diameter (cm), mean (SD)	0.2 (2.1) [b]	0.9 (2.1) [b]	.007
5-y Change in visceral fat (cm^2), mean (SD)	-7.1 (40.4) [b]	9.0 (40.4)	.001

CES-D = Center for Epidemiologic Studies Depression scale. [a] Based on X^2 tests for dichotomous and categorical variables and on independent t tests for continuous variables; for obesity variables sex-adjusted means and SD's are presented based on analyses of covariance; [b] paired-sample t tests indicated statistically significant 5-y increase or decrease in (abdominal) obesity: $p \leq .001$.

Table 2: Baseline depressive symptoms and 5-year change in obesity

	Overall obesity				Abdominal obesity					
	BMI		***Percent body fat***		***waist circumference***		***sagittal diameter***		***visceral fat***	
	N = 2088		*N = 1944*		*N = 2067*		*N = 1885*		*N = 1752*	
Depressive symptoms	β	P	β	p	β	p	β	p	β	p
Continuous CES-D score										
Sociodemographics [a]	.037	.09	.012	.59	.028	.16	.048	.04	.045	.06
+ Overall obesity [b]	-	-	-	-	.032	.07	.044	.05	.045	.05
+ Life style and diseases [c]	.035	.11	.007	.76	.026	.15	.037	.10	.042	.08
Depression: CES-D ≥ 16										
Sociodemographics [a]	.033	.13	.003	.88	.034	.08	.061	.006	.079	.001
+ Overall obesity [b]	-	-	-	-	.034	.05	.057	.008	.079	.001
+ Life style and diseases [c]	.030	.18	-.002	.94	.031	.08	.054	.01	.080	.001

CES-D = Center for Epidemiologic Studies Depression scale. [a] Linear regression analyses adjusted for corresponding baseline obesity measure, sex, age, race, site and education; [b] previous model plus baseline BMI for abdominal obesity measures; [c] previous model plus smoking status, alcohol intake, physical activity, prevalent diabetes, prevalent cardiovascular disease, number of other chronic diseases and number of prescription medications taken.

Role of weight change

To check whether depressive symptoms were also associated with a loss in abdominal obesity, an adjusted multinomial logistic regression analysis was performed using visceral fat change categories (≥ 30% loss, no change, ≥ 30% gain) as the outcome. Persons with baseline depression had odds of 0.43 (95% CI = 0.18-1.04, p = .06; i.e. a decreased risk) to lose visceral fat and odds of 2.06 (95% CI = 1.04-4.05, p = .04; i.e. an increased risk) to gain visceral fat compared with having no change in visceral fat, indicating a linear association between baseline depression and change in visceral fat. To verify that the association between depression and visceral fat was independent of change in BMI, the association between depression and visceral fat, as reported in Table 2, was additionally adjusted for change in BMI. The relationship between depression and change in visceral fat remained statistically significant (β = .050, p= .009). Furthermore, no interaction between depression and change in BMI in the association with visceral fat was found (p = .95).

Sex and race differences

To examine whether associations between depression and abdominal obesity were consistent across sex and race, sex by depression and sex-specific race by depression interaction terms were included in the fully adjusted models assessing the association between depression and change in abdominal obesity as described in Table 2. A significant sex by depression interaction (p = .03) was found for change in visceral fat only. No race

interactions were found for men (all $p > .20$), but in women, trends for race by depression interactions in predicting 5-year change in abdominal obesity were found for waist circumference ($p = .06$), sagittal diameter ($p = .09$), and visceral fat ($p = .08$). Because race interactions were found in women only, subsequent analyses were stratified by sex and race. Depression rates across sex by race groups were as follows: white men (N = 683): 3.5%, white women (N = 645): 4.3%, black men (N = 304): 3.3%, and black women (N = 456): 4.8%. Stratification showed that the association between depression and 5-year change in visceral fat was generally consistent across sex and race with the exception of black women (white men: $\beta = .154$, $p < .001$; white women: $\beta = .078$, $p = .05$; black men: $\beta = .121$, $p = .06$; black women: $\beta = -.029$, $p = .54$). To graph these findings for all abdominal obesity measures, adjusted mean 5-year changes in abdominal obesity were calculated for persons with and without baseline depression using analyses of covariance stratified by sex and race (Figure 1). The figure shows that baseline depression was associated with an increase in abdominal obesity while persons without depression showed a much smaller increase or even a decrease in abdominal obesity over 5 years. This finding was consistent across all abdominal obesity measures and across sex and race, with the exception of black women.

Additional analyses

To assess the robustness of our findings, a set of sensitivity analyses was conducted. First, the association between depression and change in abdominal obesity was assessed in persons with a single depression at baseline (N = 17) and in those with persistent/recurrent depression (N = 67). These analyses showed rather consistent associations for both depression groups (waist circumference: $\beta = .016$, $p = .36$ and $\beta = .027$, $p = .13$, sagittal diameter: $\beta = .028$, $p = .21$ and $\beta = .047$, $p = .03$, visceral fat: $\beta = .070$, $p = .002$ and $\beta = .055$, $p = .02$, respectively). To ensure that associations between depression and increases in abdominal fat were not due to antidepressant use, the analyses described in Table 2 were additionally adjusted for antidepressant use, which did not change the results in any meaningful way. Similar results were also found when adjusting for other psychoactive medications. Also, when persons with a low quality of repositioning on the CT scans (N = 84) were excluded from the analyses, associations with increases in visceral fat were comparable. Finally, to include all persons with baseline obesity data and to check the potential effect of selective drop-out, analyses were conducted after multiple imputation for missing values. When repeating the fully adjusted analyses described in Table 2, associations between depression and change in abdominal obesity largely remained (waist circumference: N = 3038, $\beta = .021$, $p = .27$; sagittal diameter: N = 2998, $\beta = .041$, $p = .03$; visceral fat: N = 2931, $\beta = .073$, $p < .001$).

Discussion

This study examined whether depressive symptoms could predict an increase in abdominal obesity over time in a large community-based sample of older persons. As hypothesized, depressed persons showed a significantly greater increase in abdominal obesity over 5 years, especially in visceral fat, than non-depressed persons. Such an association was not

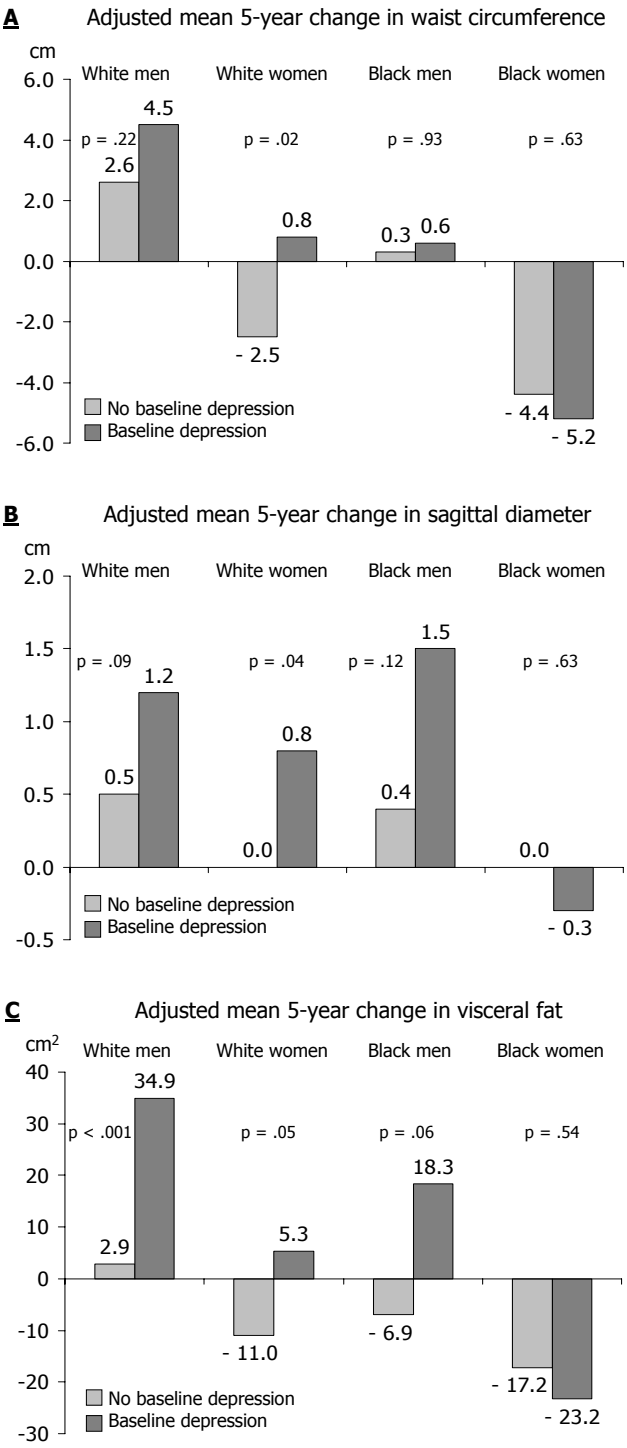
A
Adjusted mean 5-year change in waist circumference
cm
White men
White women
Black men
Black women
6.0
4.0
2.0
0.0
-2.0
-4.0
-6.0
p = .22
p = .02
p = .93
p = .63
2.6
4.5
0.8
0.3
0.6
- 2.5
- 4.4
- 5.2
No baseline depression
Baseline depression
B
Adjusted mean 5-year change in sagittal diameter
cm
White men
White women
Black men
Black women
2.0
1.5
1.0
0.5
0.0
-0.5
p = .09
p = .04
p = .12
p = .63
0.5
1.2
0.0
0.8
0.4
1.5
0.0
- 0.3
No baseline depression
Baseline depression
C
Adjusted mean 5-year change in visceral fat
cm2
White men
White women
Black men
Black women
40
30
20
10
0
-10
-20
-30
p < .001
p = .05
p = .06
p = .54
2.9
34.9
5.3
- 11.0
- 6.9
18.3
- 17.2
- 23.2
No baseline depression
Baseline depression

Figure 1. Adjusted mean 5-year changes in abdominal obesity according to baseline depression across sex and race groups

Waist circumference (**A**; overall p = .08), sagittal diameter (**B**; overall p = .01), and visceral fat (**C**; overall p= .001); based on analyses of covariance adjusted for corresponding baseline abdominal obesity measure, age, site, education, body mass index, smoking status, alcohol intake, physical activity, prevalent diabetes, prevalent cardiovascular disease, number of other chronic diseases and number of prescription medications taken.

found for an increase in overall obesity and also appeared to be independent of changes in overall obesity, suggesting that depressive symptoms are rather specifically associated with fat gain in the visceral region.

To our knowledge, this is the first study to examine the association between depressive symptoms and increases in abdominal obesity over time in a large cohort. Our results are consistent with a study by Weber-Hamann et al.,[25] that showed a larger accumulation of visceral fat mass over time in 29 depressed patients compared with 17 controls. Most studies so far have assessed the association between abdominal obesity and depression cross-sectionally, using either anthropometric measures alone, or CT measures in relatively small study samples.[19-24] Most of these studies showed a positive relationship between depression and abdominal obesity, although one large epidemiological study could not demonstrate an association between waist circumference and depression.[34] In our study, associations with waist circumference were also weaker than those with visceral fat, possibly owing to the fact that waist circumference is only an indirect measure of visceral fat and is determined by both abdominal subcutaneous and visceral fat mass. Also, measuring waist circumference might be less precise than CT scanning. Stronger associations were found for sagittal diameter, which is considered a better indicator of visceral fat than waist circumference in older persons.[35] Our results indeed show a higher correlation of sagittal diameter (r = 0.75) than waist circumference (r = 0.63) with visceral fat. Most pronounced, however, were the associations with visceral fat, which is in line with our hypothesis that depressive symptoms contribute to an accumulation of visceral fat specifically.

Although depression has been associated with weight loss,[30,31] our results show an increase in visceral fat in persons with depressive symptoms, even in this aging population where decreases in fat mass are common.[36] We found no evidence that depression would result in a loss of visceral fat. In fact, we found that depression was negatively associated with a loss of visceral fat, indicating that depression is linearly linked with the accumulation of visceral fat and no U-shaped association exists. Furthermore, depression appeared to be specifically associated with abdominal obesity stronger than and independent of overall obesity. Associations between depressive symptoms and overall obesity were not found, and adjusting abdominal obesity analyses for baseline BMI did not influence findings. We additionally adjusted for change in BMI which was partly an over-adjustment because changes in BMI also reflect changes in visceral fat. However, despite this relatively strict adjustment, the relationship between depression and change in visceral fat remained. Moreover, our results showed that across the whole range of weight change, an association existed between depression and visceral fat, suggesting that even in persons who lost

weight, visceral fat was preferentially retained in those with depression. The finding that associations were specific for abdominal obesity is in line with other studies showing that abdominal obesity, more than overall obesity, is associated with poor health outcomes such as diabetes, CVD, and mortality.[15-18] Because depression as well as diabetes and CVD appear to be specifically associated with excess visceral fat, this could help explain the frequently found increased risk of diabetes and CVD in depressed persons.

Our results indicate that depression predicts increases in abdominal obesity in all but black women. Reasons for this exception are not entirely clear. One explanation may be that the black women in this older sample experienced a relatively large decrease in visceral fat, which might have obscured the association between depressive symptoms and the accumulation of visceral fat. Alternatively, this could have been a chance finding due to small sample sizes after stratification by sex and race. However, expected associations were found for the other 3 sex by race groups. Future research should explore sex and race differences further in younger samples.

What are the mechanisms by which depression may promote visceral fat accumulation? As suggested by Björntorp, stress activates the HPA-axis, which leads to an accumulation of visceral fat.[13] Studies show that chronic stress and depression are, at least in a subset of patients, associated with a dysregulation of the HPA-axis and elevated concentrations of cortisol.[7,8] Visceral fat is highly sensitive to cortisol owing to a high density of glucocorticoid receptors.[14] Cortisol promotes the accumulation of visceral fat by activating lipoprotein lipase and inhibiting lipid mobilization.[13] Indeed, it has been shown that hypercortisolemic depression is associated with abdominal obesity.[20,37] Moreover, these effects might be most pronounced when levels of sex steroid hormones, which have been found to reduce visceral fat mass and have a lipid-mobilizing effect,[13,38] are low, as has been observed in late-life depression.[9] Further, depression has been linked to high levels of inflammatory markers,[10] which can activate the HPA-axis[39] and therefore subsequently result in visceral obesity. Moreover, as described by Gold and Chrousos,[40] even in persons with non-hypercortisolemic atypical depression, owing to overeating, a cycling of weight gain and loss occurring throughout recurrent episodes of depression could preferentially distribute weight to visceral fat areas. An alternative explanation for why depression may lead to abdominal obesity is that depressed persons have an unhealthier lifestyle. Although we adjusted our analyses for some lifestyle behaviors (smoking status, alcohol intake, and physical activity), it is possible that depressed persons have a poorer dietary pattern. However, a poor diet in itself would likely lead to an increase in both overall and abdominal obesity.[41] In combination with a hyperactive HPA-axis, however, it is possible that excess caloric intake is preponderantly stored into visceral fat depots.[42] In addition, somatic comorbidities of depressed persons could have led to the increase in visceral fat, although our results were little affected by adjustment for diabetes, CVD, and general health status. Furthermore, weight gain in depressed persons has been associated with the use of antidepressants.[43] However, in our study antidepressant use was not associated with increases in (abdominal) obesity, and therefore our findings can not be the result of antidepressant use.

The link between depressive symptoms and increased abdominal obesity was stronger for the dichotomous indicator of depression than for the continuous CES-D score, suggesting

that a certain amount of distress is needed before visceral fat starts to accumulate. On the other hand, we did not find evidence that the association between depression and an increase in abdominal obesity was specific for persons with persistent/recurrent depression compared with persons with a single depression episode at baseline. However, most persons depressed at baseline did have an additional episode of depression during follow-up and it is possible that persons only depressed at baseline did experience additional depressive episodes between annual assessments.

Our study has some limitations. We did not have well-accepted criterion-based psychiatric diagnoses of depression. However, the CES-D is a commonly used scale to measure clinically relevant depressive symptoms. Our results might have been even stronger for persons with a diagnosis of major depressive disorder. Further, our sample showed low levels of depressive symptomatology at baseline and this aging population exhibited little change or even decrease in obesity, making it more difficult to detect associations with changes in obesity. Possibly, associations may be even stronger in a middle-aged population were visceral fat tends to increase over time. In addition, after 5 years of follow-up, there was drop-out owing to mortality and non-response, likely resulting in a relatively healthy sample, which could have led to an underestimation of the association between depression and change in abdominal obesity. On the other hand, studying the most healthy had the advantage that associations found were less likely confounded by somatic comorbidities. When missing values of persons without 5-year follow-up data were imputed, thereby including the less healthy, associations between depression and increase in abdominal obesity largely remained. Our study also has some important strengths, including use of a large community-based cohort followed up for several years with repeated DXA and CT scans, which provide more direct assessments of total and visceral fat stores, as well as the more commonly used anthropometric measures.

Our longitudinal results suggest that clinically relevant depressive symptoms give rise to an increase in abdominal obesity, in particular visceral fat, which seems to be stronger than and independent of overall obesity. Because of this specific accumulation of visceral fat, these results clearly suggest that there may be certain underlying pathophysiological mechanisms, plausibly involving the HPA-axis, which link depression with visceral fat. This could also help explain why depression is often followed by diabetes or CVD. Future research should further disentangle these mechanisms because this will yield important information for prevention or treatment of depression-related health consequences.

Acknowledgements

We thank David Vergouw for his help with the multiple imputation analyses. This study was supported by contracts N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106 from the National Institute on Aging (NIA); a travel grant from the Young Academy of the Royal Netherlands (Ms Vogelzangs); and in part by the Intramural Research Program of the National Institutes of Health, NIA. Data analyses were supported by grant R01-HL72972-01 from the National Heart, Lung, and Blood Institute.

References

1. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry.* 1999;174:307-311.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet.* 1997;349:1498-1504.
3. Penninx BW, Guralnik JM, Mendes de Leon CF et al. Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age. *Am J Cardiol.* 1998;81:988-994.
4. Penninx BW, Beekman AT, Honig A et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry.* 2001;58:221-227.
5. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia.* 2006;49:837-845.
6. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. *JAMA.* 2006;295:2874-2881.
7. Deuschle M, Weber B, Colla M, Depner M, Heuser I. Effects of major depression, aging and gender upon calculated diurnal free plasma cortisol concentrations: a re-evaluation study. *Stress.* 1998;2:281-287.
8. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992;267:1244-1252.
9. Morsink LF, Vogelzangs N, Nicklas BJ et al. Associations between sex steroid hormone levels and depressive symptoms in elderly men and women: Results from the Health ABC study. *Psychoneuroendocrinology.* 2007;32:874-883.
10. Penninx BW, Kritchevsky SB, Yaffe K et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiatry.* 2003;54:566-572.
11. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA.* 1999;282:2131-2135.
12. Bjorntorp P, Rosmond R. Neuroendocrine abnormalities in visceral obesity. *Int J Obes Relat Metab Disord.* 2000;24 Suppl 2:S80-S85.
13. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev.* 2001;2:73-86.
14. Bronnegard M, Arner P, Hellstrom L, Akner G, Gustafsson JA. Glucocorticoid receptor messenger ribonucleic acid in different regions of human adipose tissue. *Endocrinology.* 1990;127:1689-1696.
15. Ohlson LO, Larsson B, Svardsudd K et al. The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in the study of men born in 1913. *Diabetes.* 1985;34:1055-1058.
16. Folsom AR, Kaye SA, Sellers TA et al. Body fat distribution and 5-year risk of death in older women. *JAMA.* 1993;269:483-487.
17. Rexrode KM, Carey VJ, Hennekens CH et al. Abdominal adiposity and coronary heart disease in women. *JAMA.* 1998;280:1843-1848.
18. Nicklas BJ, Penninx BWJH, Cesari M et al. Association of visceral adipose tissue with incident myocardial infarction in older men and women: the Health, Aging and Body Composition Study. *Am J Epidemiol.* 2004;160:741-749.
19. Thakore JH, Richards PJ, Reznek RH, Martin A, Dinan TG. Increased intra-abdominal fat deposition in patients with major depressive illness as measured by computed tomography. *Biol Psychiatry.* 1997;41:1140-1142.
20. Weber-Hamann B, Hentschel F, Kniest A et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. *Psychosom Med.* 2002;64:274-277.
21. Ahlberg AC, Ljung T, Rosmond R et al. Depression and anxiety symptoms in relation to anthropometry and metabolism in men. *Psychiatry Res.* 2002;112:101-110.
22. Lee ES, Kim YH, Beck SH, Lee S, Oh SW. Depressive mood and abdominal fat distribution in overweight premenopausal women. *Obes Res.* 2005;13:320-325.
23. Kahl KG, Bester M, Greggersen W et al. Visceral fat deposition and insulin sensitivity in depressed women with and without comorbid borderline personality disorder. *Psychosom Med.* 2005;67:407-412.
24. Eskandari F, Mistry S, Martinez PE et al. Younger, premenopausal women with major depressive disorder have more abdominal fat and increased serum levels of prothrombotic factors: implications for greater cardiovascular risk. *Metabolism.* 2005;54:918-924.

25. Weber-Hamann B, Werner M, Hentschel F et al. Metabolic changes in elderly patients with major depression: evidence for increased accumulation of visceral fat at follow-up. *Psychoneuroendocrinology.* 2006;31:347-354.
26. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.
27. Beekman AT, Deeg DJ, van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med.* 1997;27:231-235.
28. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med.* 1994;10:77-84.
29. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol.* 1994;10:405-411.
30. Haukkala A, Uutela A, Salomaa V. Depressive symptoms, clinical hostility, and weight change: A 3-year follow-up among middle-aged men and women. *Int J Behav Med.* 2001;8:116-133.
31. Forman-Hoffman VL, Yankey JW, Hillis SL, Wallace RB, Wolinsky FD. Weight and depressive symptoms in older adults: direction of influence? *J Gerontol B Psychol Sci Soc Sci.* 2007;62:S43-S51.
32. Van Buuren, S and Oudshoorn, CGM. mice: Multivariate Imputation by Chained Equations. 2007. Ref Type: Internet Communication
33. Visser M, Pahor M, Tylavsky F et al. One- and two-year change in body composition as measured by DXA in a population-based cohort of older men and women. *J Appl Physiol.* 2003;94:2368-2374.
34. Hach I, Ruhl UE, Klotsche J, Klose M, Jacobi F. Associations between waist circumference and depressive disorders. *J Affect Disord.* 2006;92:305-308.
35. Harris TB, Visser M, Everhart J et al. Waist circumference and sagittal diameter reflect total body fat better than visceral fat in older men and women. The Health, Aging and Body Composition Study. *Ann N Y Acad Sci.* 2000;904:462-473.
36. Newman AB, Lee JS, Visser M et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr.* 2005;82:872-878.
37. Vogelzangs N, Suthers K, Ferrucci L et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology.* 2007;32:151-159.
38. Villareal DT, Holloszy JO. Effect of DHEA on abdominal fat and insulin action in elderly women and men: a randomized controlled trial. *JAMA.* 2004;292:2243-2248.
39. Kyrou I, Chrousos GP, Tsigos C. Stress, visceral obesity, and metabolic complications. *Ann N Y Acad Sci.* 2006;1083:77-110.
40. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry.* 2002;7:254-275.
41. Newby PK, Muller D, Hallfrisch J, Qiao N, Andres R, Tucker KL. Dietary patterns and changes in body mass index and waist circumference in adults. *Am J Clin Nutr.* 2003;77:1417-1425.
42. Dallman MF, la Fleur SE, Pecoraro NC, Gomez F, Houshyar H, Akana SF. Minireview: glucocorticoids--food intake, abdominal obesity, and wealthy nations in 2004. *Endocrinology.* 2004;145:2633-2638.
43. Zimmermann U, Kraus T, Himmerich H, Schuld A, Pollmacher T. Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res.* 2003;37:193-220.

Chapter 6

Obesity and onset of significant depressive symptoms

Results from a prospective community-based cohort study of older men and women

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Journal of Clinical Psychiatry 2009; Dec 15. Epub ahead of print

Abstract

Objective

Although several cross-sectional studies have linked obesity and depression, less is known about their longitudinal association and about the relative influence of obesity subtypes. We prospectively examined whether obesity (specifically, abdominal) increased the risk of onset of depression in a population-based sample of older persons.

Method

Participants were 2547 non-depressed, well-functioning white and black persons, aged 70-79 years, enrolled in the Health, Aging and Body Composition study, an ongoing prospective community-based cohort study. Baseline measurements were conducted between April 1997 and June 1998. Overall obesity was assessed by body mass index (BMI) and percent body fat (measured by dual energy x-ray absorptiometry), whereas abdominal obesity measures included waist circumference, sagittal diameter, and visceral fat (measured by computer tomography). Onset of significant depressive symptoms was defined as a Center for Epidemiologic Studies Depression 10-item score ≥ 10 at any annual follow-up over 5 years and/or new antidepressant medication use. Persistent depression was defined as depression at 2 consecutive follow-up visits.

Results

Over 5 years, significant depressive symptoms emerged in 23.7% of initially non-depressed persons. In men, both overall (BMI: HR per SD increase = 1.20, 95% CI = 1.03-1.40) and abdominal obesity (visceral fat: HR per SD increase = 1.19, 95% CI = 1.07-1.33) predicted onset of depressive symptoms after adjustment for sociodemographics. When BMI and visceral fat were adjusted for each other, only visceral fat was significantly associated with depression onset (HR = 1.18, 95% CI = 1.04-1.34). Stronger associations were found for persistent depressive symptoms. No associations were found in women.

Conclusion

This study shows that obesity, in particular visceral fat, increases the risk of onset of significant depressive symptoms in men. These results suggest that specific mechanisms might relate visceral fat to the onset of depression.

Introduction

In a recent systematic review of epidemiological studies Atlantis and Baker[1] concluded there is a weak level of evidence that obesity increases the incidence of depression, predominantly based on cross-sectional studies.[2-4] The prevalence of overweight and obesity is increasing worldwide at an alarming rate.[5] In the US, obesity is prevalent among almost one-third of the general population, and another third is overweight.[6] Overweight and obesity are associated with a multitude of health risks, including increased risks of diabetes and cardiovascular disease (CVD).[7,8] This combination of high prevalence and poor outcomes makes obesity a major public health concern with implications for depression outcomes, as well. At this moment, however, depression guidelines do not consider obesity as a major comorbidity of depression. Before obesity comorbidity can be incorporated in depression treatment, it is important to gain more knowledge of the direction, specifics, and strength of the association between obesity and depression.

Longitudinal studies that examine the direction of the association between depression and obesity are relatively sparse, were mostly conducted among adolescents, and show mixed results. Recently, we showed that depression is associated with an increase in obesity over time.[9] Conversely, one study showed that obesity was associated with subsequent depression,[10] but this was not confirmed in another study.[11] In addition, sex inconsistencies in the obesity-depression relationship have been found.[1-3,11,12] Furthermore, different subtypes of obesity exist, and the location of excess fat storage may be an important determinant of subsequent health risks. Excess fat in the visceral region has been found to be a stronger predictor of diabetes and CVD than overall obesity.[13,14] Longitudinal studies on the association between abdominal obesity and depression are even more sparse.

The present study investigated prospectively whether obesity predicted the onset of significant depressive symptoms in an older sample of initially non-depressed persons. In addition, this study examined whether the association between obesity and onset of depressive symptoms was consistent for men and women, and whether type of obesity (overall versus abdominal) influenced the obesity-depression link.

Methods

Study Population

The Health, Aging and Body Composition (ABC) study is an ongoing prospective cohort study among 3075 well-functioning white and black men and women, aged 70-79 years. The Health ABC study was designed to prospectively investigate changes in body composition and weight-related health outcomes in an aging population. Participants were recruited between April 1997 and June 1998 from a random sample of white and black Medicare-eligible beneficiaries residing in the areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. Eligible subjects reported no difficulty with walking for a quarter of a mile, walking up 10 steps, or performing activities of daily living. Subjects were ineligible if they had severe difficulty communicating, active cancer treatment in the past 3 years, or plans to move. After complete description of the study, all participants signed an informed written consent approved by the institutional review boards of the clinical sites. For the present study, only persons free of depression at baseline were selected (N =

2802). Of these, persons without data on baseline body mass index (BMI) or visceral fat (N = 104) or with no follow-up data on depressive symptoms (N = 151) were excluded, leaving 2547 persons for the present analyses. Excluded persons were more often men (57.6% versus 48.6%, p = .006), black (52.2% versus 40.6%, p < .001), less educated (35.7% versus 43.6% with postsecondary education; p < .001), had more often onset of depressive symptoms (33.7% versus 23.9%, p = .03), and had a lower (sex-adjusted) percent body fat (33.7% versus 35.1%, p = .002) than included persons, but did not differ in age or other obesity measures.

Significant depressive symptoms

During the baseline interview and at follow-up (after 2, 3, 4, and 5 years), depressive symptoms were measured with the Center for Epidemiologic Studies Depression (CES-D) scale 10-item version, assessing depressive symptoms in the previous week.[15] The original 20-item CES-D scale has been widely used in older populations and has been shown to be a valid and reliable instrument (100% sensitivity and 88% specificity for detecting a major depressive disorder in the older population),[16] but the 10-item subset of the CES-D, ranging from 0 to 30, has shown good predictive accuracy when compared to the 20-item CES-D scale.[17] In addition, at baseline and at follow-up (after 1, 2, 4 and 5 years) all medications regularly taken in the past 2 weeks were recorded and coded according to the Iowa Drug Information System (IDIS).[18] Antidepressant use included monoamine oxidase inhibitors (IDIS code 281605), tri/tetracyclic antidepressants (IDIS code 281606), selective serotonin reuptake inhibitors (IDIS code 281607), and other antidepressants (IDIS code 281604) with depression or mood disorder as self-reported reason. Persons with antidepressant use or a CES-D-10 score ≥ 10 (compares to the commonly used cut-off of ≥ 16 on CES-D-20[17]) at baseline were excluded from the analyses. For the present analyses, onset of significant depressive symptoms was defined as having a CES-D-10 score ≥ 10 on any of the follow-up assessments and/or new antidepressant medication use during follow-up. To identify the onset of more chronic depressive symptoms, persistent depressive symptoms were defined as depressive symptoms at 2 consecutive follow-up visits. For sensitivity analyses 2 alternative definitions of depressive symptoms were constructed: one based on CES-D-10 scores only (since antidepressant medications are sometimes used in the treatment of obesity), and another incorporated an additional requirement of a minimum increase of 3 points on the CES-D-10 (to assure an actual onset of depressive symptoms and not just a crossing of the cut-off point).

Obesity

Overall obesity

Body weight was measured on a standard balance beam scale to the nearest 0.1 kg. Height was measured barefoot using a wall-mounted stadiometer to the nearest 0.1 cm. BMI was calculated as weight (kg) divided by the square of height (m^2). BMI categories were constructed to indicate normal weight (BMI < 25), overweight (BMI ≥ 25 and < 30), and obesity (BMI ≥ 30). Percent body fat was determined via a whole body dual energy x-ray absorptiometry (DXA) scan (for details, see[9]).

Abdominal obesity

Computed tomography (CT) scanning was performed at the level between the fourth and fifth lumbar vertebrae (L4-L5) to measure visceral fat (cm^2), as described in Vogelzangs et al.[9] Next to this continuous measure of visceral fat, sex-specific quartiles of visceral fat were constructed and a dichotomous visceral fat variable compared persons in the highest quartile to persons in quartiles 1 to 3. In addition to this direct CT measure of visceral fat, some anthropometric measures were assessed. Maximum sagittal diameter (cm), the distance between the abdomen and back, was derived from the CT scans. Waist circumference (cm) was measured at the largest abdominal circumference to the nearest 0.1 cm using a flexible plastic tape measure.

Covariates

Covariates were a priori selected on the basis of previously reported associations with both obesity and depression. Sociodemographic characteristics included age, sex, site (Pittsburgh, Memphis), race (white, black), marital status (yes or no currently married) and education (less than high school, high school, postsecondary). Lifestyle characteristics were also assessed, including smoking status (non, former, or current), current alcohol intake (yes or no > 1 drink per day) and physical activity (sum of weight training, high and medium intensity exercise, aerobic dance, [exercise] walking, and stair climbing [in kcal/week]). As both obesity (specifically, abdominal) and depression have consistently been associated with CVD and diabetes, these diseases were specifically addressed. Presence of baseline diabetes and CVD (including stroke, myocardial infarction, angina pectoris, coronary angioplasty or coronary artery bypass grafting) was adjudicated using standardized algorithms, considering various sources of information that included self-report, medication use, clinical examination findings, and medical claims data from the former Health Care Financing Administration. Identification of incident diabetes and new CVD events during follow-up additionally included hospitalization records assessed according to set algorithms. Also, we included 2 indicators for general health status. Number of other chronic diseases was mainly based on self-report and included congestive heart failure, peripheral arterial disease, cancer, lung disease, osteoarthritis, osteoporosis, gastrointestinal disease, prostate disease, thyroid disease, Parkinson's disease, and kidney disease. In addition, all medications regularly taken in the past 2 weeks before baseline were recorded and coded according to the Iowa Drug Information System.[18] From this inventory, the total number of prescription medication taken was calculated.

Statistical Analyses

Because sex differences in the relationship between obesity and depression have been observed[3,12] and since men and women differ in body composition, all analyses were presented for men and women separately, and sex-interaction effects were tested for statistical significance. Sample characteristics were compared between persons with and without onset of depressive symptoms during follow-up using X^2 tests for dichotomous and categorical variables and independent t tests for continuous variables. Risk of onset of significant depressive symptoms (overall, non-persistent and persistent) according to

different measures of baseline obesity (overall and abdominal) was assessed using Cox regression analyses, and the proportional hazards assumption was examined. The assumption of linearity was assessed by checking improvement of model fit after inclusion of a quadratic term for each corresponding obesity measure, respectively. Presence of multicollinearity was assessed by means of the variance inflation factor (VIF) when all covariates were included in the same model. To be able to compare hazard ratios (HRs) across obesity measures, HRs with 95% confidence intervals (CIs) were expressed per standard deviation (SD) increase. For comparability across subsamples, sex-weighted SDs were used. Analyses were adjusted for baseline CES-D-10 score, sex, age, race, site, marital status and education. Because fat distribution differs between whites and blacks, all analyses were repeated, including race-interaction terms, to test whether findings were consistent across race.

To examine whether associations between obesity and onset of significant depressive symptoms could be explained by lifestyle or disease differences at baseline, the above described Cox regression analyses were additionally adjusted for smoking status, alcohol intake, physical activity, prevalent and incident diabetes and CVD, number of other chronic diseases, and number of prescription medication taken. In order to compare the independent effects of overall and abdominal obesity, the associations between overall obesity measures and onset of depressive symptoms were adjusted for visceral fat, and the associations between abdominal obesity measures and onset of depression were adjusted for BMI.

Finally, the risks of onset of depressive symptoms and of persistent depressive symptoms were plotted for men and women across BMI categories and for men and women with high versus normal visceral fat mass, and onset rates of depressive symptoms were calculated (in percent per year). In addition, population attributable risks (PARs) of obesity (BMI $\geq$ 30) and high visceral fat ($\geq$ 194 cm^2) in men were calculated. PAR describes the percentage by which the onset rate of depressive symptoms or persistent depressive symptoms could be reduced when the risk factor would be completely eliminated. The following equation was used: PAR = p(HR-1) / (1+ p[HR-1]), where p is the prevalence of the risk factor in the population at risk.[19]

Results

The mean age of the participants was 73.6 (SD = 2.9) years, 51.4% were women and 40.6% were black. During a mean follow-up of 4.3 (SD = 1.1) years, significant depressive symptoms emerged in 23.9% (N = 609) of the initially non-depressed sample and significant persistent depressive symptoms in 7.8% (N = 198). Men experienced more diabetes and CVD, but women had a higher rate of onset of depressive symptoms. The mean BMI was comparable between men and women, however women had a higher percent body fat (40.7% versus 29.3%) than men, but had less visceral fat (132.2 versus 155.2 cm^2). Visceral fat correlated more strongly with waist circumference (Pearson's r = 0.65) and sagittal diameter (Pearson's r = 0.75) than with BMI (Pearson's r = 0.56). Table 1 shows sample characteristics for persons with and without onset of depressive symptoms during follow-up for men and women separately.

Table 1. Sample characteristics

Characteristic	Men			Women		
	Depressive symptoms during follow-up			***Depressive symptoms during follow-up***		
	No *N=988*	***Yes*** *N=250*	p [a]	***No*** *N=950*	***Yes*** *N=359*	p [a]
Sociodemographic variables						
Age (years), mean (SD)	73.6 (2.9)	73.9 (2.8)	.22	73.5 (2.9)	73.5 (2.9)	.90
Black, %	33.7	44.0	.002	43.9	48.7	.12
Memphis site, %	47.1	52.4	.13	49.4	53.2	.22
Married, %	73.0	65.6	.02	39.7	39.6	.97
Educational level, %			<.001			<.001
Less than high school	22.9	35.6		19.8	28.1	
High school	26.5	21.6		38.2	42.6	
Postsecondary	50.6	42.8		42.0	29.2	
Lifestyle variables						
Smoking status, %			.87			.28
Never	30.9	29.2		56.8	61.6	
Former	59.2	60.4		34.5	30.1	
Current	9.9	10.4		8.6	8.4	
> 1 Alcoholic drink / day, %	12.9	8.8	.08	3.7	2.8	.43
Physical activity (kcal/week), mean (SD)	1539 (2514)	1215 (1879)	.02	743 (1240)	649 (1309)	.23
Health & disease variables						
Prevalent cardiovascular disease, %	28.1	29.2	.74	16.9	23.7	.005
Prevalent diabetes, %	25.7	28.4	.39	17.9	24.8	.005
New cardiovascular event during follow-up, %	16.5	11.6	.06	8.4	9.5	.55
Incident diabetes during follow-up, %	4.6	5.2	.67	4.9	2.8	.09
Number of other chronic diseases, mean (SD)	1.4 (1.0)	1.5 (1.1)	.24	0.9 (0.9)	1.2 (1.0)	<.001
Number of prescription medication taken, mean (SD)	2.8 (2.4)	3.2 (2.7)	.02	3.0 (2.5)	3.8 (2.8)	<.001
Depression-related variables						
Baseline CES-D-10 score (0-30), mean (SD)	1.9 (2.1)	3.5 (2.6)	<.001	2.3 (2.3)	3.8 (2.6)	<.001
Onset of persistent depressive symptoms, %	*NA*	30.0	*NA*	*NA*	34.3	*NA*

CES-D = Center for Epidemiologic Studies Depression scale; NA = not applicable. [a] Based on X^2 tests for dichotomous and categorical variables and independent t tests for continuous variables.

Table 1. Continued

	Men			Women		
	No	***Yes***	p [a]	***No***	***Yes***	p [a]
Obesity variables						
Overall obesity						
Body mass index (kg/m^2), mean (SD)	27.0 (3.7)	27.5 (4.3)	.09	27.7 (5.4)	27.9 (5.4)	.52
Percent body fat, mean (SD)	29.2 (4.7)	29.7 (5.4)	.14	40.7 (5.6)	40.6 (5.9)	.87
Abdominal obesity						
Waist circumference (cm), mean (SD)	100.7 (10.3)	102.3 (11.3)	.04	97.9 (13.4)	99.0 (13.8)	.22
Sagittal diameter (cm), mean (SD)	23.6 (3.2)	24.2 (3.5)	.01	23.4 (3.5)	23.6 (3.5)	.28
Visceral fat (cm^2), mean (SD)	153.0 (68.8)	163.8 (78.7)	.05	131.8 (61.1)	133.4 (59.9)	.66

[a] Based on X^2 tests for dichotomous and categorical variables and independent t tests for continuous variables.

Table 2 shows the results of Cox regression analyses assessing the risk of onset of significant depressive symptoms according to baseline obesity among non-depressed persons at baseline. In the total sample, no associations were found for overall obesity measures, but sagittal diameter (HR per SD [3.4 cm] increase = 1.11, 95% CI = 1.02-1.20) and visceral fat (HR per SD [65.5 cm^2] increase = 1.10, 95% CI = 1.02-1.20) predicted onset of depressive symptoms after adjustment for sociodemographics. Sex-stratified analyses showed that both overall and abdominal obesity increased the risk of onset of depressive symptoms in men. For instance, risk of depressive symptoms increased by 20% for each SD (4.6 kg/m^2) increase in BMI (HR = 1.20, 95% CI = 1.03-1.40) and by 19% for each SD (65.5 cm^2) increase in visceral fat (HR = 1.19, 95% CI = 1.07-1.33) (Table 2). No associations were found in women. When tested, obesity by sex interactions were found (BMI: p = .04, percent body fat: p = .03, waist circumference: p = .04, sagittal diameter: p = .04, visceral fat: p = .06). No significant obesity by race interactions were observed among men and women (all p > .20). Similar results were found when the definition of the onset of depressive symptoms was determined without data on new antidepressant use (N with depression = 553) or when an additional requirement of a minimum 3 point increase on the CES-D-10 was incorporated (N with depression = 593). Persons with significant depressive symptoms at follow-up (based on CES-D-10), increased from a mean baseline CES-D-10 score of 3.7 (SD = 2.6) to a mean CES-D-10 score of 12.4 (SD = 2.8) during their depressed episodes. As can be seen in Table 2, additional adjustment for smoking status, alcohol intake, physical activity, prevalent and incident diabetes and CVD, number of other chronic diseases and number of prescription medication taken did not change the results in any meaningful way.

Next, to assess the effect of abdominal obesity versus overall obesity, the associations between overall obesity measures and onset of significant depressive symptoms were adjusted for visceral fat and were found to be no longer significant in men (e.g. for BMI: HR = 1.10, 95% CI = 0.93-1.32; Table 2). Alternatively, when associations between abdominal

Table 2. Risk (per SD increase [e]) of onset of significant depressive symptoms among initially non-depressed persons according to baseline obesity

	Unadjusted risk [a]		Risk adjusted for sociodemographics [b]		Risk additionally adjusted for lifestyle and diseases [c]		Risk additionally adjusted for obesity [d]	
Obesity	HR (95% CI)	P	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Total sample *(N = 2547)*			*N cases = 609*					
Overall obesity								
Body mass index	1.06 (0.99-1.15)	.11	1.04 (0.96-1.12)	.32	1.02 (0.94-1.1)0	.71	0.96 (0.87-1.06)	.41
Percent body fat	1.03 (0.95-1.12)	.42	1.04 (0.96-1.13)	.34	1.02 (0.94-1.11)	.58	0.98 (0.89-1.08)	.68
Abdominal obesity								
Waist circumference	1.11 (1.03-1.20)	.01	1.08 (0.99-1.17)	.07	1.05 (0.97-1.14)	.27	1.10 (0.95-1.27)	.19
Sagittal diameter	1.14 (1.05-1.23)	.002	1.11 (1.02-1.20)	.02	1.08 (0.99-1.17)	.09	1.23 (1.05-1.43)	.01
Visceral fat	1.10 (1.02-1.19)	.02	1.10 (1.02-1.20)	.02	1.07 (0.99-1.17)	.09	1.10 (0.99-1.22)	.06
Men (*N = 1238)*			*N cases = 250*					
Overall obesity								
Body mass index	1.18 (1.01-1.37)	.03	1.20 (1.03-1.40)	.02	1.18 (1.01-1.37)	.04	1.10 (0.93-1.32)	.27
Percent body fat	1.14 (0.99-1.31)	.08	1.19 (1.03-1.36)	.02	1.15 (1.00-1.33)	.05	1.10 (0.94-1.28)	.22
Abdominal obesity								
Waist circumference	1.20 (1.04-1.39)	.01	1.23 (1.06-1.42)	.006	1.20 (1.04-1.39)	.01	1.26 (1.04-1.52)	.02
Sagittal diameter	1.24 (1.09-1.40)	.001	1.24 (1.08-1.41)	.001	1.21 (1.06-1.38)	.004	1.31 (1.11-1.56)	.002
Visceral fat	1.16 (1.04-1.29)	.01	1.19 (1.07-1.33)	.002	1.17 (1.04-1.31)	.009	1.18 (1.04-1.34)	.009
Women (*N = 1309)*			*N cases = 359*					
Overall obesity								
Body mass index	1.03 (0.94-1.12)	.54	0.99 (0.91-1.08)	.84	0.97 (0.88-1.06)	.47	0.93 (0.83-1.03)	.16
Percent body fat	0.99 (0.90-1.09)	.82	0.97 (0.88-1.07)	.55	0.96 (0.87-1.06)	.45	0.93 (0.84-1.04)	.20
Abdominal obesity								
Waist circumference	1.07 (0.98-1.18)	.14	1.02 (0.92-1.12)	.74	0.99 (0.90-1.09)	.80	1.04 (0.89-1.21)	.66
Sagittal diameter	1.08 (0.98-1.20)	.13	1.03 (0.93-1.15)	.53	1.00 (0.90-1.11)	.98	1.12 (0.93-1.34)	.23
Visceral fat	1.05 (0.94-1.18)	.37	1.03 (0.92-1.15)	.64	1.00 (0.89-1.12)	.93	1.02 (0.88-1.17)	.83

[a] Based on Cox regression analyses adjusted for sex (total sample only); [b] additionally adjusted for baseline CES-D-10 score, age, race, site, marital status and educational level; [c] additionally adjusted for smoking status, alcohol intake, physical activity, prevalent diabetes or cardiovascular disease, incident diabetes, new cardiovascular events, number of other chronic diseases and number of prescription medication taken; [d] additionally adjusted for visceral fat (overall obesity only) and body mass index (abdominal obesity only); [e] per SD increase: 4.6 kg/m^2 for body mass index, 5.3% for percent body fat, 12.0 cm for waist circumference, 3.4 cm for sagittal diameter, and 65.5 cm^2 for visceral fat.

Table 3. Risk (per SD increase [c]) of onset of significant non-persistent and persistent depressive symptoms among initially non-depressed persons according to baseline obesity

	Non-persistent depressive symptoms				Persistent depressive symptoms			
	Risk adjusted for lifestyle and diseases [a]		Risk additionally adjusted for obesity [b]		Risk adjusted for lifestyle and diseases [a]		Risk additionally adjusted for obesity [b]	
Obesity	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Men (*N = 1238)*	*N cases = 175*				*N cases = 75*			
Overall obesity								
Body mass index	1.07 (0.89-1.29)	.49	1.03 (0.83-1.28)	.76	1.50 (1.13-1.98)	.005	1.29 (0.94-1.76)	.12
Percent body fat	1.05 (0.89-1.25)	.54	1.03 (0.85-1.24)	.76	1.50 (1.16-1.95)	.002	1.37 (1.04-1.82)	.03
Abdominal obesity								
Waist circumference	1.12 (0.94-1.34)	.20	1.23 (0.99-1.54)	.07	1.46 (1.12-1.92)	.006	1.41 (1.01-1.96)	.05
Sagittal diameter	1.14 (0.97-1.33)	.11	1.27 (1.04-1.56)	.02	1.43 (1.12-1.83)	.004	1.47 (1.08-2.01)	.01
Visceral fat	1.08 (0.94-1.25)	.27	1.10 (0.94-1.29)	.22	1.40 (1.17-1.68)	<.001	1.42 (1.17-1.73)	<.001
Women (*N = 1309)*	*N cases = 236*				*N cases = 123*			
Overall obesity								
Body mass index	0.96 (0.86-1.07)	.47	0.94 (0.82-1.07)	.35	0.96 (0.81-1.12)	.58	0.86 (0.72-1.04)	.12
Percent body fat	0.95 (0.84-1.07)	.40	0.93 (0.82-1.07)	.31	0.98 (0.82-1.16)	.80	0.91 (0.76-1.11)	.35
Abdominal obesity								
Waist circumference	1.00 (0.88-1.12)	.96	1.10 (0.91-1.34)	.32	0.94 (0.80-1.11)	.47	0.90 (0.69-1.18)	.45
Sagittal diameter	1.00 (0.87-1.14)	.95	1.17 (0.93-1.46)	.18	0.99 (0.82-1.19)	.88	1.03 (0.74-1.42)	.87
Visceral fat	0.97 (0.84-1.12)	.64	0.99 (0.84-1.18)	.94	1.02 (0.84-1.23)	.86	1.05 (0.83-1.32)	.71

[a] Based on Cox regression analyses adjusted for baseline CES-D-10 score, age, race, site, marital status, educational level, smoking status, alcohol intake, physical activity, prevalent diabetes or cardiovascular disease, incident diabetes, new cardiovascular events, number of other chronic diseases and number of prescription medication taken; [b] additionally adjusted for visceral fat (overall obesity only) and body mass index (abdominal obesity only); [c] per SD increase: 4.6 for body mass index, 5.3% for percent body fat, 12.0 cm for waist circumference, 3.4 cm for sagittal diameter, and 65.5 cm^2 for visceral fat; persons with persistent depressive symptoms were excluded from the analyses on non-persistent depressive symptoms and persons with non-persistent depressive symptoms were excluded from the analyses on persistent depressive symptoms.

obesity and onset of depressive symptoms in men were adjusted for BMI, the associations remained similar (e.g. for visceral fat: HR = 1.18, 95% CI = 1.04-1.34; Table 2). Table 3 presents fully adjusted models (with and without adjustment for obesity) with onset of non-persistent depressive symptoms and persistent depressive symptoms as the outcome. Although associations of abdominal obesity with onset of non-persistent depressive symptoms were found, obesity was more strongly associated with the more chronic indicator of depressive symptoms in men; in women associations remained absent. When tested, no indications of non-linearity or multicollinearity were found (all quadratic terms p > .05; all VIF < 2).

To graphically illustrate the association between obesity and onset of both significant depressive symptoms and persistent depressive symptoms, the cumulative onset of depressive symptoms over time adjusted for sociodemographics, lifestyle, and diseases was plotted for men and women across BMI categories (Figure 1A and 1C) and for men and women with normal (Q1-Q3) and high (Q4) visceral fat (Figure 1B and 1D). In addition, unadjusted onset rates of depressive symptoms across groups are presented in Figure 1. Obese men (BMI > 30) were at the highest risk for onset of depressive symptoms, which was statistically significant for persistent depressive symptoms (HR = 2.03, 95% CI = 1.06-3.89). Men with high visceral fat (≥ 194 cm^2) had a 1.33 increased risk (95% CI = 1.00-1.77) of becoming depressed and a 2.04 increased risk (95% CI = 1.25-3.34) of becoming persistently depressed compared to men with visceral fat < 194 cm^2. As can be seen from Figure 1, men with high visceral fat were at an equal risk of becoming depressed than women in general. In fact, the unadjusted hazard ratio of onset of depressive symptoms for women compared to men was 1.38 (95% CI =1.17-1.62) and 1.62 (95% CI = 1.22-2.16) for onset of persistent depressive symptoms, which is equal to or even lower than the hazard ratios of onset of depressive symptoms and persistent depressive symptoms due to high visceral fat in men. High BMI or visceral fat did not increase the risk of becoming depressed in women. Finally, the population attributable risks of BMI > 30 and high visceral fat adjusted for sociodemographics, lifestyle and diseases were calculated for men and found to be 7% and 8%, respectively, for onset of depressive symptoms and 17% and 19% for onset of persistent depressive symptoms. This suggests that in the entire older male population, 19% of all new cases with persistent depressive symptoms were related to having high visceral fat mass.

Discussion

This study examined whether obesity was associated with onset of significant depressive symptoms in a large community-based sample of older, initially non-depressed, persons during 5 years of follow-up. The results showed that in men, but not in women, obesity increased the risk of onset of significant depressive symptoms. Specifically, abdominal obesity appeared to be associated with the onset of depressive symptoms, independent of and more consistently than overall obesity. Men with high visceral fat had a more than 2-fold increased risk of becoming persistently depressed compared to men with normal amounts of visceral fat. Moreover, results showed that in men, almost 10% of the onsets of depressive symptoms and 20% of the onsets of persistent depressive symptoms was related to having high visceral fat.

Several studies indicated that obesity and depression are associated.[2-4] However, as concluded by Atlantis and Baker[1] in their systematic review on obesity an depression, few studies have investigated the temporal direction of this association. Our findings correspond to a study by Roberts et al.,[10] which showed among persons aged ≥ 50 years that obesity at baseline was associated with an increased risk of depression 5 years later. Our results additionally showed that associations with depressive symptoms appear to be more consistently related to abdominal obesity than to overall obesity. The association between depressive symptoms and overall obesity in men was not consistently found after

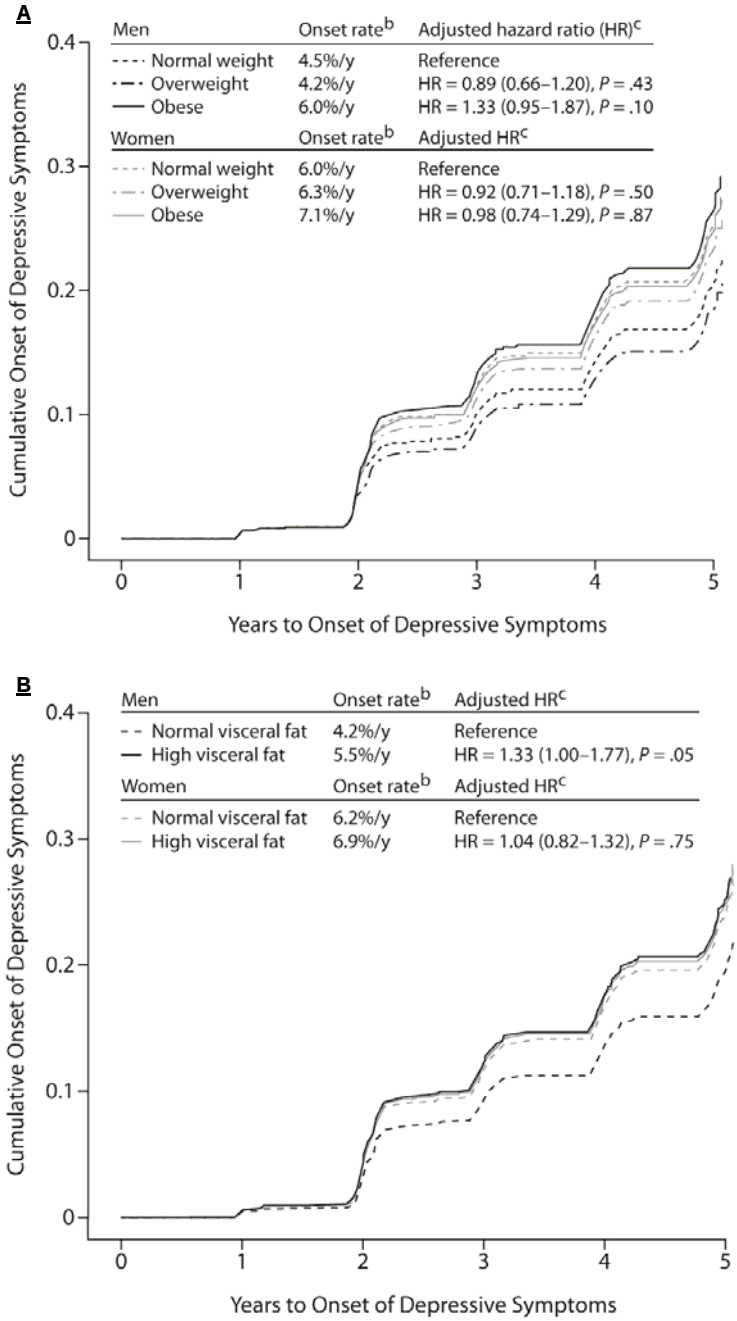

Figure 1. Cumulative onset of depressive symptoms according to sex and **A**) BMI categories; **B**) visceral fat status.

[a] Unadjusted rates; [b] based on Cox regression analyses adjusted for baseline CES-D-10 score, age, race, site, marital status, educational level, smoking status, alcohol intake, physical activity, prevalent diabetes or cardiovascular disease, incident diabetes, new cardiovascular events, number of other chronic diseases, number of prescription medication taken.

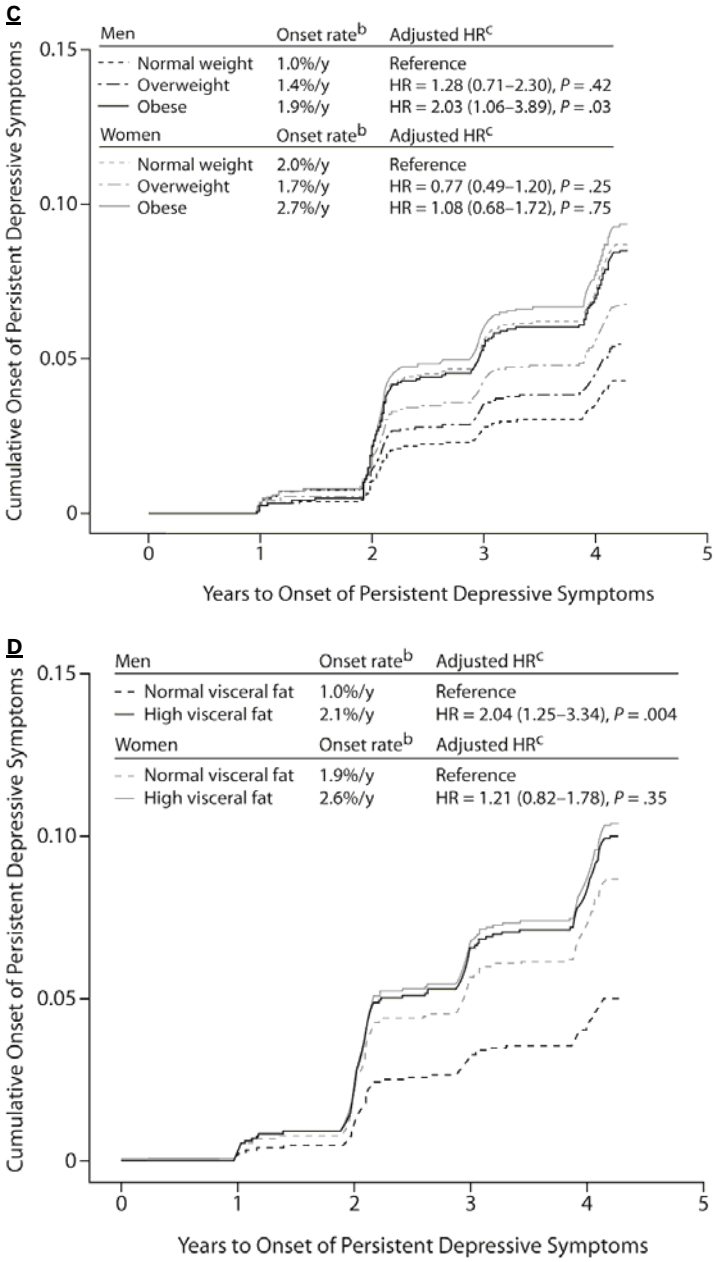

Figure 1. Cumulative onset of persistent depressive symptoms according to sex and **C**) BMI categories; **D**) visceral fat status.

Persons with non-persistent depressive symptoms were excluded from the analyses. [a] Unadjusted rates; [b] based on Cox regression analyses adjusted for baseline CES-D-10 score, age, race, site, marital status, educational level, smoking status, alcohol intake, physical activity, prevalent diabetes or cardiovascular disease, incident diabetes, new cardiovascular events, number of other chronic diseases, number of prescription medication taken.

adjustment for visceral fat, while the association with visceral fat remained after controlling for BMI. At least, these results show that abdominal obesity has an additional effect on onset of depressive symptoms above the influence of overall obesity. These results are in line with other studies showing that, in particular, abdominal obesity, more than overall obesity, is associated with poor health outcomes, such as diabetes and CVD.[13,14]

To our knowledge, the current study was the first to test and demonstrate that abdominal obesity increases the risk of onset of significant depressive symptoms in men. This evidence should be considered together with other recent longitudinal results that illustrate - the other way around - that depressive symptoms also lead to increases in abdominal obesity over 5 years.[9] The fact that abdominal obesity and depressive symptoms are found to be reciprocally associated indicates that the two are strongly intertwined and suggests that a vicious cycle might exist. The bidirectional relationship between abdominal obesity and depressive symptoms further indicates that when trying to break this vicious cycle, treatment of either obesity or depression cannot be given in isolation and comorbidity between these two should be taken into consideration.

How might abdominal obesity increase the risk of incident depression? First, a poor self-image or perceived stigma of an obese person might induce depression.[20] Also, binge-eating behavior, not uncommon in obese persons, has been associated with major depressive disorder.[21] These mechanisms are probably true for overall obesity as well as and not specific for abdominal obesity. Poor lifestyle behaviors might lead to both abdominal obesity and depression. However, in our analyses, adjustment for lifestyle behaviors did not influence results much. In addition, diseases related to abdominal obesity such as diabetes and CVD have been associated with depression[22,23] and might be responsible for the association between abdominal obesity and depression. In our study, adjustment for prevalent as well as incident diabetes and CVD did not affect the relationship between abdominal obesity and the onset of depressive symptoms, suggesting that such an association does exist rather independently of diabetes and CVD. Other pathophysiological explanations may exist. Studies have shown that visceral fat produces cytokines in higher amount than subcutaneous fat.[24] High levels of cytokines such as TNF-alpha, IL-6, and C-reactive protein have been found both in visceral obesity[25] and depression.[26] In addition, the mechanisms discussed above (poor lifestyle, more diabetes and CVD, and inflammation in obese persons) might all induce vascular damage and are, therefore, in line with the vascular depression hypothesis, which states that vascular damage in the brain might predispose, precipitate, or perpetuate depression in the elderly.[27] Other linking mechanisms could be a dysregulation of the hypothalamic-pituitary-adrenal axis[28,29] or diminished functioning of sex steroid hormones[30,31] as these mechanisms have been linked to both abdominal obesity and depression.

The link between abdominal obesity and significant depressive symptoms was restricted to men. A reason for this could be due to the fact that men have more visceral fat than women. If the amount of visceral fat is important for negative health effects to emerge, than men will be more at risk to experience such negative health effects. In addition, this is an aging population in which losses of fat (including visceral fat) over time are not uncommon, especially in women,[32] which might leave women at a smaller risk of visceral fat

to cause poor health. Another explanation might be that, in women, the relative contribution of visceral fat to depression onset is small due to a larger influence of competing risk factors. For instance, insufficient social support and stressful life events have been found to pose a greater risk for depression among women compared to men.[33,34] Although previous cross-sectional studies that examined sex differences predominantly showed stronger results for women in the association between overall obesity and depression,[3,12] one study reported an association between depression and abdominal obesity only in men.[2] Future research should explore these sex differences further in younger samples to eliminate counteracting effects of aging.

Our study has some limitations. We did not have well-defined DSM-IV-based depression diagnoses. However, the CES-D is a commonly used scale to assess clinically significant depressive symptoms. In addition, since we had no information on history of depression, onset of depressive symptoms might represent recurrence of an earlier depression in life. Therefore, results do not necessarily indicate incidence of a first depression episode in life, which is less common in later life, but do reflect a new occurrence of depressive symptoms during later life. Our study also had some important strengths including a large sample with longitudinal assessments of depressive symptoms. In addition, DXA and CT scans were performed, which assess total and visceral fat stores directly, and we were able to compare them with more commonly used anthropometric measures.

In all, our findings indicate that the strength of the association between abdominal obesity and depressive symptoms is of both clinical and public health relevance. Men with visceral fat levels in the highest quartile (≥194 cm^2) had almost a 35% greater chance of becoming depressed over 5 years than men with normal amounts of visceral fat. The risk of becoming persistently depressed was more than 2-fold for men with high visceral fat. We found that the size of this effect was at least equal to the difference in the onset rate of depressive symptoms between men and women. A 35-40% increased risk of incident depression for women versus men is comparable to what has been found in other studies among older persons[35] and is normally considered to be an important predictor for depression onset. In contrast to sex, however, high visceral fat is potentially modifiable, and it is tempting to consider the possibility that weight reduction might reduce the onset of new depressive symptoms. Future research should investigate whether visceral fat reduction indeed can prevent onset of depressive symptoms.

In conclusion, our results suggest that, in older men, obesity relates to the onset of significant depressive symptoms. Abdominal obesity appears to be more consistently associated with onset of depressive symptoms than overall obesity or at least shows an additional effect above overall obesity. These findings strengthen the idea that specific properties of visceral fat might give rise to depression. The impact of the association between abdominal obesity and onset of significant depressive symptoms on public mental health seems to be of great enough importance to warrant additional research that confirms our findings and explores underlying mechanisms. When these mechanisms are known, this might have direct implications for depression treatment and prevention.

Acknowledgements

This work was supported by National Institute on Aging (NIA) contract numbers N01-AG-6-2101, N01-AG-6-2103, and N01-AG-6-2106 and in part by the Intramural Research Program of the National Institutes of Health, NIA. Data analyses were supported by grant R01-HL72972-01 from the National Heart, Lung, and Blood Institute (NHLBI). The work of NV was supported by a travel grant from the Young Academy of the Royal Netherlands Academy of Arts and Science.

References

1. Atlantis E, Baker M. Obesity effects on depression: systematic review of epidemiological studies. *Int J Obes (Lond).* 2008;32:881-891.
2. Herva A, Laitinen J, Miettunen J et al. Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. *Int J Obes (Lond).* 2006;30:520-527.
3. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* 2003;158:1139-1147.
4. Simon GE, Von KM, Saunders K et al. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry.* 2006;63:824-830.
5. World health Organization. Obesity. Preventing and managing the global epidemic. Report of a WHO consultation on obesity. 894. 2000. Geneva, WHO. Technical Report Series. Ref Type: Report
6. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA.* 2006;295:1549-1555.
7. Harris TB, Launer LJ, Madans J, Feldman JJ. Cohort study of effect of being overweight and change in weight on risk of coronary heart disease in old age. *BMJ.* 1997;314:1791-1794.
8. NIH. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults: the evidence report. 1998. USA, US Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute. Ref Type: Report
9. Vogelzangs N, Kritchevsky SB, Beekman AT et al. Depressive symptoms and change in abdominal obesity in older persons. *Arch Gen Psychiatry.* 2008;65:1386-1393.
10. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes Relat Metab Disord.* 2003;27:514-521.
11. Forman-Hoffman VL, Yankey JW, Hillis SL, Wallace RB, Wolinsky FD. Weight and depressive symptoms in older adults: direction of influence? *J Gerontol B Psychol Sci Soc Sci.* 2007;62:S43-S51.
12. Carpenter KM, Hasin DS, Allison DB, Faith MS. Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. *Am J Public Health.* 2000;90:251-257.
13. Despres JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ.* 2001;322:716-720.
14. Nicklas BJ, Penninx BWJH, Cesari M et al. Association of visceral adipose tissue with incident myocardial infarction in older men and women: the Health, Aging and Body Composition Study. *Am J Epidemiol.* 2004;160:741-749.
15. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.
16. Beekman AT, Deeg DJ, van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med.* 1997;27:231-235.
17. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med.* 1994;10:77-84.
18. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. *Eur J Epidemiol.* 1994;10:405-411.

19. Smit F, Beekman A, Cuijpers P, de GR, Vollebergh W. Selecting key variables for depression prevention: results from a population-based prospective epidemiological study. *J Affect Disord.* 2004;81:241-249.
20. Chen EY, Bocchieri-Ricciardi LE, Munoz D et al. Depressed mood in class III obesity predicted by weight-related stigma. *Obes Surg.* 2007;17:669-671.
21. Grucza RA, Przybeck TR, Cloninger CR. Prevalence and correlates of binge eating disorder in a community sample. *Compr Psychiatry.* 2007;48:124-131.
22. Brown LC, Majumdar SR, Newman SC, Johnson JA. History of depression increases risk of type 2 diabetes in younger adults. *Diabetes Care.* 2005;28:1063-1067.
23. Penninx BW, Guralnik JM, Mendes de Leon CF et al. Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age. *Am J Cardiol.* 1998;81:988-994.
24. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab.* 1998;83:847-850.
25. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Pract.* 2005;69:29-35.
26. Penninx BW, Kritchevsky SB, Yaffe K et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiatry.* 2003;54:566-572.
27. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry.* 1997;54:915-922.
28. Vogelzangs N, Suthers K, Ferrucci L et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology.* 2007;32:151-159.
29. Weber-Hamann B, Hentschel F, Kniest A et al. Hypercortisolemic depression is associated with increased intra-abdominal fat. *Psychosom Med.* 2002;64:274-277.
30. Bjorntorp P, Rosmond R. Neuroendocrine abnormalities in visceral obesity. *Int J Obes Relat Metab Disord.* 2000;24 Suppl 2:S80-S85.
31. Morsink LF, Vogelzangs N, Nicklas BJ et al. Associations between sex steroid hormone levels and depressive symptoms in elderly men and women: results from the Health ABC study. *Psychoneuroendocrinology.* 2007;32:874-883.
32. Newman AB, Lee JS, Visser M et al. Weight change and the conservation of lean mass in old age: the Health, Aging and Body Composition Study. *Am J Clin Nutr.* 2005;82:872-878.
33. Kendler KS, Myers J, Prescott CA. Sex differences in the relationship between social support and risk for major depression: a longitudinal study of opposite-sex twin pairs. *Am J Psychiatry.* 2005;162:250-256.
34. Maciejewski PK, Prigerson HG, Mazure CM. Sex differences in event-related risk for major depression. *Psychol Med.* 2001;31:593-604.
35. Norton MC, Skoog I, Toone L et al. Three-year incidence of first-onset depressive syndrome in a population sample of older adults: the Cache County study. *Am J Geriatr Psychiatry.* 2006;14:237-245.

Chapter 7

Metabolic depression: a chronic depressive subtype

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Submitted

Abstract

Context

Several studies report a cross-sectional association between metabolic syndrome and depression. Possibly, metabolic syndrome promotes onset or chronicity of depression. However, such a longitudinal link has not yet been confirmed.

Objective

To examine whether metabolic syndrome and its components are associated with onset and chronicity of depression during 6 years of follow-up.

Design

The InCHIANTI study, an ongoing prospective cohort study with 6 years of follow-up.

Setting

Community-dwelling older persons from the Chianti area, Italy.

Participants

A total of 823 persons aged ≥ 65 years.

Main Outcome Measures

Metabolic syndrome was assessed at baseline and defined as three or more of the following: abdominal obesity, high triglycerides, low high-density lipoprotein cholesterol, high blood pressure, and high fasting glucose. Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression (CES-D) scale at baseline and after 3 and 6 years of follow-up.

Results

At baseline, 202 persons (24.5%) had metabolic syndrome, and 168 (20.4%) were depressed (CES-D ≥ 20). Among non-depressed persons, 26.0% developed depression. Higher waist circumference increased odds of depression onset (adjusted OR per SD increase = 1.31, 95% CI = 1.08-1.59), but there was no association between other metabolic syndrome components or metabolic syndrome and onset of depression. Among depressed persons, depression had a chronic character in 69.0% of persons without and 88.5% of persons with metabolic syndrome. Metabolic syndrome was associated with an almost 3-fold increased odds of chronicity of depression after adjustment for sociodemographics, lifestyle and health factors (OR = 2.71, 95% CI = 1.00-7.33), with almost every metabolic syndrome component contributing to this association.

Conclusions

In late life, waist circumference, but not metabolic syndrome, predicted onset of depression. Depressed persons with metabolic syndrome were more likely to have persistent or recurrent depression. The latter may suggest that depression with metabolic abnormalities ('metabolic depression') identifies a chronic subtype of depression.

Introduction

Depression and cardiovascular disease are leading causes of disease burden worldwide and their relative impact on public health will continue to increase.[1] Substantial evidence supports an association between these harmful disorders.[2,3] Gaining knowledge on the underlying mechanisms to comorbidity of disease could direct prevention and treatment strategies. Over the past few years metabolic syndrome - a combination of cardiovascular risk factors, including abdominal obesity, lipid abnormalities, hypertension, and hyperglycemia[4] - has become a key topic of interest as a possible link between depression and cardiovascular disease.[5]

Recent cross-sectional studies indicate a link between depression and metabolic syndrome,[6-14] although some negative findings have been reported too.[15-17] Insight into cause and consequence between these disorders is still very limited as only few studies have assessed the temporal direction of the association between depression and metabolic syndrome.[18-23] Three studies in middle-aged persons demonstrated that depressive symptoms predicted onset of metabolic syndrome.[21-23] However, to improve both prevention and treatment of depression it is essential to know whether metabolic syndrome could initiate and/or perpetuate depression. Two studies in middle-aged populations[18,19] and one in an older population[20] showed an increased risk of depressive symptoms onset for persons with the metabolic syndrome. To our knowledge, no previous study has examined whether metabolic syndrome is a prognostic factor of chronicity of depression in older persons.

In older persons, metabolic syndrome as a precursor of depression has been suggested to be supportive of the vascular depression hypothesis,[24] which states that vascular lesions in the brain - that might be caused by metabolic disturbances - give rise to depressive symptoms. It is however very well possible that metabolic disturbances in themselves give rise to depression. In line with this, we have previously shown that abdominal obesity, a central component in metabolic syndrome, predicted the new onset of significant depressive symptoms over 5 years.[25] Even stronger associations were found with the onset of more persistent depressive symptoms. This last finding suggests that metabolic syndrome might continue to promote depressive symptoms after they have emerged, resulting in more chronic depression.

Therefore, the aims of the present study were to examine in a community-based sample of older persons whether metabolic syndrome and its components were associated with (1) onset of depression in depression-free persons at baseline, and (2) chronicity of depression in persons already presenting with depression at baseline.

Methods

Study sample

Participants were part of the InCHIANTI study, a prospective population-based study of older persons. From 1998 to 2000, the study sample was randomly selected from the population registry of two sites in Italy: Greve in Chianti and Bagno a Ripoli, using a multistage stratified sampling method. Baseline data collection consisted of a home interview and a medical evaluation at the study clinic, which took place within 21 days after the home interview. Follow-up assessments were performed three and six years after the

baseline visit. The Italian National Institute of Research and Care on Aging ethical committee approved the study protocol and all respondents signed informed consent. A more detailed description of the study design is given elsewhere.[26]

The InCHIANTI study consisted of 1155 participants aged 65 and over, but because of missing data on metabolic syndrome (N = 54), depression status at baseline (N = 4) or during follow-up (N = 274), the present study included data from 823 participants. Excluded persons were significantly older (80.1 versus 73.3 years, $p < .001$), were less educated (4.4 versus 5.6 years, $p < .001$) and were more likely to have depression at baseline (28.5% versus 20.4%, $p = .007$) than included persons. No significant baseline differences in sex, number of chronic diseases or metabolic syndrome were found between in- and excluded persons.

Depression

Depressive symptoms were assessed at baseline and after 3 years and 6 years of follow-up using the Center for Epidemiological Studies-Depression (CES-D) scale, a widely used self-report scale to assess depressive symptoms in the past week.[27] The original 20-item version, ranging from 0-60 points, was used and filled in during the home interview. The CES-D-20 has been shown to be a valid instrument for identifying depression in community-dwelling older adults[28] and in Italian persons.[29] In our study, the internal consistency was high: Cronbach alpha = 0.82. Onset of depression was defined as having no depression at baseline (CES-D < 20), but having a CES-D ≥ 20 after three or six years of follow-up. Chronicity of depression was defined as having a CES-D ≥ 20 both on baseline and on at least one of the follow-up assessments (year three or year six). In line with other research, overestimation in this older and Italian population was avoided by using the cut-off of 20 (as opposed to 16) as indication of depression.[13] Although scoring above a depressive symptoms cut-off does not necessarily imply depression, in this paper for convenience we will refer to CES-D ≥ 20 as depression. Also, we cannot be sure whether a depression was persistent or recurrent. For convenience, we refer to this as chronic depression because it does suggest a chronic character of the depression.

Metabolic syndrome

Metabolic syndrome was defined as the presence of three or more of the following criteria: (i) abdominal obesity (waist circumference > 102 cm in men or > 88 cm in women); (ii) hypertriglyceridemia (triglyceride level ≥ 150 mg/dl); (iii) low high-density lipoprotein (HDL) cholesterol (< 40 mg/dl in men or < 50 mg/dl in women); (iv) high blood pressure (systolic/diastolic blood pressure ≥ 160/90 mmHg, and/or currently using anti-hypertensive medication); (v) high fasting glucose (≥ 110 mg/dl and/or currently using anti-diabetic medication). These criteria are similar to those outlined by the National Cholesterol Education Program Adult Treatment Panel III,[4] with a minor modification for hypertension as 92% of the InCHIANTI respondents met the original blood pressure criterion (130/85 mmHg). In order to take into account the characteristics of the older study population and to only classify those participants who were definitively hypertensive the diagnostic cut-off was raised to 160/90 mmHg as done in other aging studies.[30]

During the medical evaluation, after a fasting period of at least 8 hours, a 60 ml blood sample was drawn, stored in cold glass tubes, and delivered within two hours to a central laboratory. Serum glucose, HDL cholesterol, and triglycerides were measured by standard laboratory methods. Waist circumference was measured by trained examiners at the largest mid-body point. Three blood pressure measurements were taken using a standard mercury sphygmomanometer with the respondent in a supine position; the average of the last two readings was used in this analysis. Drugs taken in the previous two weeks were identified and coded using the Anatomical Therapeutic Chemical system to ascertain anti-diabetic and anti-hypertensive medication use. In addition to a dichotomous indicator of metabolic syndrome and a count of the number of criteria met, analyses were also conducted with continuous measures of metabolic syndrome components in order to investigate the consistency over and the importance of individual components. To incorporate medication use into the continuous metabolic syndrome component measures, as done previously,[13,31] 10 and 5 mmHg was added to systolic and diastolic blood pressure, respectively, for persons using antihypertensive medication since these values represent the average decline in blood pressure in antihypertensive medication trials.[32,33] Similarly, persons who used anti-diabetic medication and had a glucose level below 126 mg/dl (the usual cut-off to identify diabetes), were given a value of 126 for fasting glucose, as done before.[13]

Covariates

Covariates were a priori selected based on previously reported associations with both metabolic syndrome and depression. Sociodemographic factors included age, sex and years of education. Life style and health factors included baseline smoking status (non-, former, or current smoker), alcohol intake (< 3 or ≥ 3 drinks a day), and number of chronic diseases (including diabetes, cardiovascular disease, cancer, liver disease, gastrointestinal disease, congestive heart failure, Parkinson's disease, peripheral arterial disease, lung disease, hip fracture, herniated disc, arthritis, osteoporosis, and cognitive deterioration). Cardiovascular disease and diabetes were also considered separately and were adjudicated based on information from self-reported history, medical exam data, hospital discharge records and medication use. Other diseases were self-reported only. In addition, onset of new cardiovascular events during follow-up was assessed based on similarly adjudicated information.

Statistical analyses

Sample characteristics were compared between persons with and without depression at baseline using X^2 and t test statistics. Logistic regression analyses were conducted separately in persons without and with depression at baseline to test whether metabolic syndrome at baseline could predict onset and chronicity of depression at follow up, respectively. Analyses were performed unadjusted, adjusted for sociodemographics (age, sex, years of education) and additionally adjusted for health indicators (smoking status, alcohol intake, number of chronic diseases). As some previous studies showed sex differences in the association between metabolic syndrome and depression,[23,34] a sex by metabolic syndrome interaction term was entered into the fully-adjusted logistic regression

analyses to assess whether findings were consistent for men and women. To test whether associations with onset or chronicity of depression were consistent across all components of metabolic syndrome, a series of fully adjusted logistic regression analyses was conducted with each metabolic syndrome component entered as predictor separately. Lastly, an additional logistic regression analysis tested the association between number of metabolic syndrome components, as an indication of severity of metabolic disturbances, and onset or chronicity of depression.

Results

Mean age of the participants was 73.3 (SD = 6.2) years, 55.9% were women, 24.5% had metabolic syndrome and 20.4% were depressed at baseline. Table 1 shows baseline characteristics for persons without and with depression at baseline. Persons with baseline depression were somewhat older, more often women, less often smoker, drank less alcohol, and had more chronic diseases. Also, persons with depression at baseline had lower glucose levels, but more often metabolic syndrome. During the 6-year follow-up, 26.0% of the initially non-depressed persons (N = 655) experienced onset of depression and 75.0% of the initially depressed persons (N = 168) had a chronic depression.

Onset of depression was assessed in persons non-depressed at baseline (N = 655). Of those without metabolic syndrome 24.2% had developed depression at follow-up, compared to 32.0% of those with metabolic syndrome. Table 2 describes the results of logistic regression analyses assessing the association between metabolic syndrome (components) and onset of depression in non-depressed persons at baseline. Although metabolic syndrome showed a trend for increased likelihood of depression onset in the unadjusted model (OR = 1.48, 95% CI = 0.99-2.20), after adjustment for sociodemographics, lifestyle and diseases this association completely disappeared (OR = 1.07, 95% CI =0.69-1.66). No indication of a sex by metabolic syndrome interaction was found (p interaction = .79). When examining separate metabolic syndrome components, waist circumference was associated with increased odds of depression onset during follow-up (OR per SD increase = 1.31, 95% CI = 1.08-1.59). This association was not mediated by new cardiovascular events during follow-up (N = 72), as adjustment for this variable did not change the OR (OR per SD increase = 1.32, 95% CI = 1.08-1.60, p = .006). When persons with diabetes or cardiovascular disease at baseline (N = 144) were excluded, the association between waist circumference and depression onset became somewhat stronger (OR per SD increase = 1.50, 95% CI = 1.18-2.15, p = .001). None of the other components, nor the sum of the components, resulted in increased risks of depression onset. To verify that these findings were not distorted by persons who merely crossed the cut-off of 20 on the CES-D from baseline to follow-up, the above analyses were repeated among persons with a CES-D score below 16 (in stead of below 20) at baseline (N = 567), such that onset of depression represented a relevant increase in depressive symptoms. This did not change findings importantly (e.g. metabolic syndrome: fully adjusted OR = 1.24, 95% CI = 0.76-2.01, p = .40; waist circumference: fully adjusted OR = 1.25, 95% CI = 1.00-1.56, p = .05).

Chronicity of depression was assessed within persons depressed at baseline (N = 168). When metabolic syndrome was not present, 69.0% of persons experienced chronic

Table 1. Sample characteristics according to depression at baseline

Characteristic	***No depression*** *N = 655*	***Depression*** *N = 168*	p [a]
Sociodemographics			
Age (years), mean (SD)	72.7 (6.0)	75.3 (6.3)	<.001
Women, %	50.7	76.2	<.001
Education (years), mean (SD)	5.7 (3.2)	5.3 (3.3)	.08
Health indicators			
Smoking			<.001
Non-smoker, %	54.2	72.6	
Former smoker, %	30.4	16.7	
Current smoker, %	15.4	10.7	
Alcohol use (≥ 3 drinks a day), %	12.5	6.0	.02
Baseline cardiovascular disease, %	12.2	10.1	.45
Baseline diabetes, %	12.7	10.1	.37
Number of chronic diseases, mean (SD)	1.2 (1.0)	1.5 (1.1)	.02
New cardiovascular event during follow-up, %	11.0	9.5	.58
Metabolic syndrome			
Waist circumference (cm), mean (SD)	93.2 (9.9)	92.0 (10.7)	.16
Triglycerides (mg/dl), mean (SD)	130.2 (74.1)	125.4 (62.3)	.43
HDL cholesterol (mg/dl), mean (SD)	55.9 (14.5)	56.8 (14.6)	.48
Systolic blood pressure (mmHg), mean (SD)	153.7 (20.4)	154.7 (20.1)	.57
Diastolic blood pressure (mmHg), mean (SD)	85.8 (9.1)	86.5 (9.1)	.40
Glucose (mg/dl), mean (SD)	97.2 (24.9)	91.4 (21.4)	.007
Metabolic syndrome, %	22.9	31.0	.03
Number of components, mean (SD)	1.7 (1.2)	1.8 (1.2)	.31
Depression			
Depressed during follow-up, %	26.0	75.0	<.001

HDL = high-density lipoprotein. [a] Based on X^2 tests for dichotomous and categorical variables and independent t tests for continuous variables.

depression compared to 88.5% when metabolic syndrome was present. Results of logistic regression analyses examining the association between metabolic syndrome (components) and chronicity of depression are presented in Table 3. Metabolic syndrome strongly predicted chronicity of depression (unadjusted OR = 3.45, 95% CI = 1.35-8.81), even after adjustment for sociodemographics, lifestyle and diseases (OR = 2.71, 95% CI = 1.00-7.33). Further adjustment for new cardiovascular events during follow-up (N = 16) did not change this finding (OR = 2.73, 95% CI = 1.01-7.39, p = .05). The association between metabolic syndrome and chronicity of depression was similarly present in both men and women

Table 2. Metabolic syndrome and onset of depression in persons non-depressed at baseline *(N = 655)*

Metabolic syndrome	OR	95%CI	p
Metabolic syndrome [a]	1.48	0.99-2.20	.06
Metabolic syndrome [b]	1.24	0.82-1.88	.32
Metabolic syndrome [c]	1.07	0.69-1.66	.76
Waist circumference [c]	1.31	1.08-1.59	.006
Triglycerides [c]	1.09	0.92-1.30	.33
High-density lipoprotein cholesterol [c]	0.92	0.76-1.12	.39
Systolic blood pressure [c]	0.93	0.77-1.12	.43
Diastolic blood pressure [c]	0.90	0.75-1.09	.27
Glucose [c]	1.04	0.87-1.24	.69
Number of metabolic syndrome components [c]	1.00	0.85-1.17	.97

Based on logistic regression analyses [a] unadjusted, [b] adjusted for age, sex, and years of education, and [c] additionally adjusted for smoking status, alcohol intake, and number of chronic diseases; ORs are given per SD increase; waist circumference: SD = 10.0 cm; triglycerides: SD = 71.9 mg/dl; HDL cholesterol: SD = 14.5 mg/dl; systolic blood pressure: SD = 20.4 mmHg; diastolic blood pressure: SD = 9.1 mmHg; glucose: SD = 24.3 mg/dl.

Table 3. Metabolic syndrome and persistence of depression in persons depressed at baseline *(N = 168)*

Metabolic syndrome	OR	95%CI	p
Metabolic syndrome [a]	3.45	1.35-8.81	.01
Metabolic syndrome [b]	3.18	1.22-8.31	.02
Metabolic syndrome [c]	2.71	1.00-7.33	.05
Waist circumference [c]	1.39	0.95-2.01	.09
Triglycerides [c]	1.61	0.90-2.88	.11
High-density lipoprotein cholesterol [c]	0.72	0.49-1.06	.10
Systolic blood pressure [c]	1.21	0.82-1.80	.34
Diastolic blood pressure [c]	1.31	0.90-1.92	.16
Glucose [c]	1.02	0.63-1.66	.93
Number of metabolic syndrome components [c]	1.66	1.16-2.38	.005

Based on logistic regression analyses [a] unadjusted, [b] adjusted for age, sex, and years of education, and [c] additionally adjusted for smoking status, alcohol intake, and number of chronic diseases; ORs are given per SD increase; waist circumference: SD = 10.0 cm; triglycerides: SD = 71.9 mg/dl; HDL cholesterol: SD = 14.5 mg/dl; systolic blood pressure: SD = 20.4 mmHg; diastolic blood pressure: SD = 9.1 mmHg; glucose: SD = 24.3 mg/dl.

(p interaction = .81). Exclusion of persons who already had diabetes or cardiovascular disease at baseline (N = 30) did not importantly affect findings (OR = 3.33, 95% CI = 0.99-11.18, p = .05). Examining different metabolic syndrome components showed that not one component was specifically associated with chronicity of depression: all components - except glucose - showed an expected increased (or decreased for HDL cholesterol) odds of chronic depression, although these relationships were not statistically significant. A logistic regression analysis with number of metabolic syndrome components as predictor indicated that odds of chronicity of depression increased with 66% for each additional component of metabolic syndrome a person had (OR = 1.66, 95% CI = 1.16-2.38).

Discussion

The present study is to our knowledge the first to examine both onset and chronicity of depression in relation to metabolic syndrome in a community-based sample of older persons. The results show that abdominal obesity, but not metabolic syndrome as a whole, predicts onset of depression. Once depressed, metabolic syndrome increases odds of remaining depressed or having recurrent episodes by almost 3-fold. These results are indicative of the existence of a chronic depressive subtype associated with metabolic disturbances which could be labeled 'metabolic depression'.

Onset of depression was predicted by large waist circumference, but not metabolic syndrome and its other components. These results are not completely in line with two recent studies in middle-aged persons and one in older persons, as these studies reported a link between metabolic syndrome as a whole and new depression onset.[18-20] Differences in study characteristics (age range, general health status, duration of follow-up) might play a role in the found discrepancies. However, the specific association for waist circumference is striking. Abdominal obesity is often regarded as a key component of the metabolic syndrome[35] and previous reports have suggested that waist circumference might be the most important metabolic syndrome feature in relation with depression.[6,11,13,18] Our results are in agreement with these and other findings from an older population-based study, which show that abdominal obesity, as indicated by high levels of visceral fat, are associated with onset of depressive symptoms.[25] Moreover, results from that same study also indicated - the other way around - an association between depressive symptoms and an increase in visceral fat over time,[36] emphasizing that in fact a vicious cycle might exist between abdominal obesity and depression.

To our knowledge, it has not been examined before whether metabolic syndrome negatively affects depression prognosis. Our results clearly show that depression associated with metabolic syndrome is less likely to resolve. Although the rate of chronic depression in this older population was already high among persons without metabolic syndrome (about 70%), it was even noticeably higher among those with metabolic syndrome (about 90%). This was reflected in an almost 3-fold increased adjusted odds of persistent or recurrent depression, which strongly indicates the chronic character of depression in the presence of metabolic syndrome. These findings were not restricted to a specific metabolic abnormality. Although most metabolic syndrome components by themselves were not significantly associated with chronicity of depression, possibly due to limited power in the smaller

depressed group, all of the metabolic syndrome components, except glucose levels, pointed in the direction of harmful disturbances. Moreover, a count of number of metabolic syndrome components was strongly associated with chronicity of depression, indicating that (almost) every component contributed to heightened likelihood of a chronic depression character. It is unclear why no effect for glucose levels was found, but previous studies have reported a lack of association between glucose levels and depressive symptoms.[6,11-13] Nevertheless, our findings that metabolic disturbances are associated with a more chronic course of depression are in line with recent findings in older men showing that abdominal obesity, in particular visceral fat, predicts onset of persistent depressive symptoms, even more strongly than onset of non-persistent depressive symptoms.[25] In addition, another recent study showed that men with metabolic syndrome were more likely to have experienced long-term depressive symptoms,[34] although it was not examined whether metabolic syndrome was more strongly associated with long-term than with short-term depressive symptoms.

Considering both our and earlier results, it seems that depression and metabolic syndrome are intertwined and represent a chronic depressive subtype. Depression and abdominal obesity might stimulate each other's occurrence, but once both present, multiple progressive metabolic abnormalities may arise, worsening depression as well as metabolic outcome more and more. These results are indicative of a distinct condition, which might be labeled 'metabolic depression'. Metabolic abnormalities as a defining component in depressive disorders have been suggested before.[37] The idea of a specific metabolic depressive subtype is further supported by recent findings from the Netherlands Study of Depression and Anxiety, which used data-driven techniques to identify depressive subtypes.[38] This study distinguished three depressive subtypes of which only one, characterized by atypical symptoms, was associated with metabolic syndrome. The possible existence of a metabolic depression clearly opens up opportunities for prevention and treatment of both depression and metabolic syndrome. Recognizing that metabolic disturbances are hampering remission from depression raises the possibility that treating metabolic abnormalities could in fact stimulate remission.

Which mechanisms may underlie this interconnection between metabolic syndrome and (chronic) depression? Possible mechanisms include inflammatory processes, hyperactivity of the hypothalamic-pituitary-adrenal (HPA)-axis, autonomic nervous system (ANS) dysfunction, and diminished functioning of the hypothalamic-pituitary-gonadal axis, as these have all been associated with both depression[39-42] and metabolic syndrome.[13,17,43-46] Further, the leptin hypothesis suggests that insufficiency or resistance of the adipose-derived hormone leptin forms a link between depression and obesity,[47] and might therefore also be involved in the relationship between depression and metabolic syndrome. Another possibility is the vascular depression hypothesis, which states that vascular damage in the brain might predispose, precipitate, or perpetuate depression in the elderly.[24] This vascular damage may be caused by continuing influence of metabolic abnormalities, HPA-axis disturbances, ANS dysfunction or chronic low-grade inflammation. Our results show that metabolic syndrome and depression are also related in the absence of overt vascular disease as adjustments for diabetes and (intermediate) cardiovascular events did not change our findings. Although

subclinical vascular damage may still be present, metabolic disturbances without having yet caused profound vascular damage might very well be sufficient on their own to produce depressive symptoms.

Our study has some important strengths. It prospectively examined the association between metabolic syndrome and depression. This study made use of a large community-based sample and was able to investigate both onset and chronicity of depression. Also, besides examining metabolic syndrome as one unified condition, associations with different metabolic syndrome components were explored as well. Some limitations have to be acknowledged too. First, we used a self-report scale to assess depressive symptoms, which do not necessarily represent psychiatric diagnoses. However, the CES-D is a well-described and valid instrument in older populations.[28,29] In addition, this study could not differentiate between recurrent or persistent depression, but the results do indicate a more chronic character of depression in persons who additionally have metabolic syndrome. Also, we had no information on history of depression, thus some of the depression-free persons at baseline might have had experienced depressive periods in the past.

To conclude, the results of the present study show that the central metabolic syndrome component, abdominal obesity, is an important risk factor for new onset of depression. Once persons are depressed, more widespread metabolic disturbances, such as present in metabolic syndrome, are highly indicative of persistent or recurrent depression. In concert with other research findings, these findings strongly indicate that depression with metabolic abnormalities ('metabolic depression') identifies a chronic depressive subtype. It is to be examined whether treatment of metabolic disturbances could improve depression prognosis.

Acknowledgements

The InCHIANTI study was supported as a targeted project (ICS 110.1/RS97.71) by the Italian Ministry of Health and in part by the US National Institute on Aging (263 MD 916413 and 263 MD 821336). Data analyses were supported through grant 1R01-HL972972 from the National Heart, Lung and Blood Institute.

References

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3:e442.
2. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J.* 2006;27:2763-2774.
3. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry.* 2007;22:613-626.
4. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation.* 2002;106:3143-3421.
5. Vitaliano PP, Scanlan JM, Zhang J, Savage MV, Hirsch IB, Siegler IC. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosom Med.* 2002;64:418-435.
6. Dunbar JA, Reddy P, vis-Lameloise N et al. Depression: an important comorbidity with metabolic syndrome in a general population. *Diabetes Care.* 2008;31:2368-2373.

7. Gil K, Radzillowicz P, Zdrojewski T et al. Relationship between the prevalence of depressive symptoms and metabolic syndrome. Results of the SOPKARD Project. *Kardiol Pol.* 2006;64:464-469.
8. Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom Med.* 2004;66:316-322.
9. McCaffery JM, Niaura R, Todaro JF, Swan GE, Carmelli D. Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. *Psychosom Med.* 2003;65:490-497.
10. Skilton MR, Moulin P, Terra JL, Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. *Biol Psychiatry.* 2007;62:1251-1257.
11. Takeuchi T, Nakao M, Nomura K, Yano E. Association of metabolic syndrome with depression and anxiety in Japanese men. *Diabetes Metab.* 2009;35:32-36.
12. Vaccarino V, McClure C, Johnson BD et al. Depression, the metabolic syndrome and cardiovascular risk. *Psychosom Med.* 2008;70:40-48.
13. Vogelzangs N, Suthers K, Ferrucci L et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology.* 2007;32:151-159.
14. Vogelzangs N, Beekman AT, Kritchevsky SB et al. Psychosocial risk factors and the metabolic syndrome in elderly persons: findings from the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci.* 2007;62:563-569.
15. Herva A, Rasanen P, Miettunen J et al. Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. *Psychosom Med.* 2006;68:213-216.
16. Hildrum B, Mykletun A, Midthjell K, Ismail K, Dahl AA. No association of depression and anxiety with the metabolic syndrome: the Norwegian HUNT study. *Acta Psychiatr Scand.* 2009;120:14-22.
17. Vogelzangs N, Beekman AT, Dik MG et al. Late-life depression, cortisol, and the metabolic syndrome. *Am J Geriatr Psychiatry.* 2009;17:716-721.
18. Akbaraly TN, Kivimaki M, Brunner EJ et al. Association between metabolic syndrome and depressive symptoms in middle-aged adults: results from the Whitehall II study. *Diabetes Care.* 2009;32:499-504.
19. Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Vanhala M. Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry.* 2008;69:178-182.
20. Mast BT, Miles T, Penninx BW et al. Vascular disease and future risk of depressive symptomatology in older adults: findings from the Health, Aging, and Body Composition study. *Biol Psychiatry.* 2008;64:320-326.
21. Goldbacher EM, Bromberger J, Matthews KA. Lifetime history of major depression predicts the development of the metabolic syndrome in middle-aged women. *Psychosom Med.* 2009;71:266-272.
22. Raikkonen K, Matthews KA, Kuller LH. Depressive symptoms and stressful life events predict metabolic syndrome among middle-aged women: a comparison of World Health Organization, Adult Treatment Panel III, and International Diabetes Foundation definitions. *Diabetes Care.* 2007;30:872-877.
23. Vanhala M, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Koponen H. Depressive symptoms predispose females to metabolic syndrome: a 7-year follow-up study. *Acta Psychiatr Scand.* 2009;119:137-142.
24. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry.* 1997;54:915-922.
25. Vogelzangs N, Kritchevsky SB, Beekman AT et al. Obesity and onset of significant depressive symptoms: results from a community-based cohort of older men and women. *J Clin Psychiatry.* 2009;in press.
26. Ferrucci L, Bandinelli S, Benvenuti E et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc.* 2000;48:1618-1625.
27. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.

28. Beekman AT, Deeg DJ, van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med.* 1997;27:231-235.
29. Fava GA. Assessing depressive symptoms across cultures: Italian validation of the CES-D self-rating scale. *J Clin Psychol.* 1983;39:249-251.
30. Ferrucci L, Guralnik JM, Pahor M et al. Apolipoprotein E epsilon 2 allele and risk of stroke in the older population. *Stroke.* 1997;28:2410-2416.
31. Licht CM, de Geus EJ, Seldenrijk A et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertension.* 2009;53:631-638.
32. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 1991;265:3255-3264.
33. Tannen RL, Weiner MG, Marcus SM. Simulation of the Syst-Eur randomized control trial using a primary care electronic medical record was feasible. *J Clin Epidemiol.* 2006;59:254-264.
34. Viinamaki H, Heiskanen T, Lehto SM et al. Association of depressive symptoms and metabolic syndrome in men. *Acta Psychiatr Scand.* 2009;120:23-29.
35. Carr DB, Utzschneider KM, Hull RL et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes.* 2004;53:2087-2094.
36. Vogelzangs N, Kritchevsky SB, Beekman AT et al. Depressive symptoms and change in abdominal obesity in older persons. *Arch Gen Psychiatry.* 2008;65:1386-1393.
37. McIntyre RS, Soczynska JK, Konarski JZ et al. Should Depressive Syndromes Be Reclassified as "Metabolic Syndrome Type II"? *Ann Clin Psychiatry.* 2007;19:257-264.
38. Lamers F, De Jonge P, Nolen WA et al. Depressive subtypes in a large cohort study: results from the NESDA study. *J Clin Psychiatry.* 2009;in press.
39. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med.* 2009;71:171-186.
40. Vreeburg SA, Hoogendijk WJ, van Pelt J et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry.* 2009;66:617-626.
41. Licht CM, de Geus EJ, Zitman FG, Hoogendijk WJ, Van DR, Penninx BW. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch Gen Psychiatry.* 2008;65:1358-1367.
42. Morsink LF, Vogelzangs N, Nicklas BJ et al. Associations between sex steroid hormone levels and depressive symptoms in elderly men and women: results from the Health ABC study. *Psychoneuroendocrinology.* 2007;32:874-883.
43. Devaraj S, Singh U, Jialal I. Human C-reactive protein and the metabolic syndrome. *Curr Opin Lipidol.* 2009;20:182-189.
44. Tentolouris N, Argyrakopoulou G, Katsilambros N. Perturbed autonomic nervous system function in metabolic syndrome. *Neuromolecular Med.* 2008;10:169-178.
45. Maggio M, Lauretani F, Ceda GP et al. Association between hormones and metabolic syndrome in older Italian men. *J Am Geriatr Soc.* 2006;54:1832-1838.
46. Maggio M, Lauretani F, Ceda GP et al. Association of hormonal dysregulation with metabolic syndrome in older women: data from the InCHIANTI study. *Am J Physiol Endocrinol Metab.* 2007;292:E353-E358.
47. Lu XY. The leptin hypothesis of depression: a potential link between mood disorders and obesity? *Curr Opin Pharmacol.* 2007;7:648-652.

Chapter 8

Urinary cortisol and 6-year risk of all-cause and cardiovascular mortality

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Submitted

Abstract

Context

The stress hormone cortisol has been linked with unfavorable cardiovascular risk factors, but longitudinal studies examining whether high levels of cortisol predict cardiovascular mortality are largely absent.

Objective

The aim of this study was to examine whether urinary cortisol levels predict all-cause and cardiovascular mortality over 6 years of follow-up in a general population of older persons.

Design

InCHIANTI study, a prospective cohort study with 6 years of follow-up.

Setting

General older population.

Participants

900 participants aged 65 years and older.

Main outcome measure

24-H urinary cortisol levels were assessed at baseline. In the following 6 years, all-cause and cardiovascular mortality was ascertained from death certificates. Cardiovascular mortality included deaths due to ischemic heart disease and cerebrovascular disease.

Results

During a mean follow-up of 5.7 (SD = 1.3) years, 207 persons died, of whom 47 from cardiovascular disease. After adjustment for sociodemographics, health indicators and baseline cardiovascular disease, urinary cortisol did not increase the risk of all-cause mortality, but did increase cardiovascular mortality risk. Persons in the highest tertile of urinary cortisol had an almost three times increased risk of dying of cardiovascular disease (HR = 2.92, 95% CI = 1.31-6.50).This effect was found to be consistent across persons with and without cardiovascular disease at baseline (p interaction = .66).

Conclusions

High cortisol levels predict cardiovascular death among both persons with and without pre-existing cardiovascular disease. The specific link with cardiovascular - and not all-cause - mortality suggests that high cortisol levels might be particularly damaging to the cardiovascular system.

Introduction

Cortisol is an important component of the stress system of the human body. In an acute physical or psychological stressful situation, the stress system becomes activated, with upregulation of the hypothalamic-pituitary-adrenal (HPA)-axis resulting in the secretion of cortisol. Direct effects of cortisol are amongst others mobilization of glucose and free fatty acids, a decrease of growth and sex hormones levels, an increase in cardiac output and blood pressure, and tempering of the activated immune system.[1-4] The function of cortisol is to help the body recover from the stress and regaining a status of homeostasis. However, chronically elevated cortisol can cause damage and dysregulation and indeed high levels of cortisol have been associated with cardiovascular risk factors, such as the metabolic syndrome and its components[5-7] and accelerated atherosclerosis.[8,9] Accordingly, studies have suggested that a chronically dysregulated cortisol response is the link between stress-related disorders, such as depression, and subsequent cardiovascular morbidity and mortality.[10,11] However, little direct evidence exists that cortisol actually increases the risk of cardiovascular end-points. A few studies among patients admitted to the hospital because of cardiac disease have shown that high cortisol levels predict subsequent events or death,[12-14] but this could well be a reflection of acute stress or disease severity.[15] Two studies reported a cortisol/testosterone ratio and a cortisol/DHEAS ratio to be predictive of incident ischemic heart disease and mortality, respectively, in middle-aged men[16] and male veterans.[17] In a general older population, cortisol was associated with increased overall mortality,[18] but since causes of death were not available, it remains unclear whether such an association was driven by cardiovascular death. Thus, although the existing literature suggests that cortisol might increase the risk of cardiovascular mortality, no study has directly tested this hypothesis. Therefore, we examined whether urinary cortisol levels predict all-cause and cardiovascular mortality over 6 years of follow-up in a general population of older persons.

Methods

Study sample

Participants were part of the InCHIANTI study, a prospective population-based study of older persons. From 1998 to 2000, the study sample was randomly selected from the population registry of two sites in Italy: Greve in Chianti, and Bagno a Ripoli, using a multistage stratified sampling method. Baseline data collection consisted of a home interview, a 24-hour urine collection and a medical evaluation at the study clinic. Follow-up visits were scheduled three and six years after the baseline visit. The study complies with the Declaration of Helsinki. The Italian National Institute of Research and Care on Aging ethical committee approved the study protocol and all respondents signed informed consent. A more detailed description of the study design is given elsewhere.[19]

The InCHIANTI study included 1155 participants aged 65 and over, but because of missing data on urinary cortisol (N = 190), or incomplete (< 20 hours) urine collection (N = 65), the present study included data from 900 participants. Excluded persons were significantly older (78.8 versus 74.5, $p < .001$), more often women (63.1% versus 54.9%, $p = .02$), and more often deceased during follow-up both from all-causes (46.3% versus 23.0%, $p < .001$) as well as from cardiovascular causes (11.0% versus 5.2%, $p < .001$).

Urinary Cortisol

The assessment of urinary cortisol over a 24-h period provides a rather stable indicator of the total cortisol excretion by the adrenals and measures the biologically active (unbound) cortisol. Before the in-clinic assessment, study participants were asked to collect all urine produced during a 24-h period starting after the first voided urine following awakening and including the first voided urine on the following day. At assessment, 10 ml aliquots of urine were prepared and stored at -80°C for later assaying at the Clinical Chemistry Laboratory of the Careggi Hospital, Italy. Urinary cortisol was measured by an immunochemiluminescence method and an ADVIA-Centaur immunoassay system (Bayer Diagnostics). The intra-assay coefficient of variation was less then 2.0% and the inter-assay coefficient of variation was less then 3.0%. Urinary cortisol level was defined as micrograms of cortisol excreted over 24 h, calculated as the concentration of cortisol (µg/ml) multiplied by the total amount of urine volume (ml) collected. The normal reference range was 28.5-213 µg cortisol excreted over 24 h. Both a continuous measure as well as a tertile categorization of urinary cortisol was used in the present study.

Mortality

Mortality data were obtained from the Mortality General Registry maintained by the Tuscany Region and from death certificates filed upon death at the registry office of the municipality of residence. Follow-up lasted from the baseline assessment until the day of death or the day of last contact and finished in 2006. Next to all-cause mortality, cardiovascular mortality was assessed based on the 9th revision of the International Classification of Diseases (ICD-9) and included death to cerebrovascular disease (ICD codes 430-438) and ischemic heart disease (ICD codes 410-414). Non-cardiovascular mortality included all other causes of death.

Covariates

Covariates were a priori selected based on previously shown association with both cortisol and mortality. Sociodemographic variables included age, sex, and years of education. Health indicators were smoking status (non-, former, or current smoker), current alcohol intake (yes or no 3 or more drinks a day) and body mass index (weight in kilograms divided by height in meters squared). Waist circumference was measured by trained examiners at the largest mid-body point. Three systolic blood pressure measurements were taken using a standard mercury sphygmomanometer with the respondent in a supine position; the average of the last two readings was used in this analysis. Depressive symptoms were assessed using the original 20-item version of the self-report Center for Epidemiologic Studies-Depression Scale administered during the home interview.[20] Cognitive functioning was assessed by means of the Mini-Mental State Examination score.[21] As a global indicator of poor physical health, number of chronic diseases (including diabetes, cancer, liver disease, gastrointestinal disease, congestive heart failure, Parkinson's disease, peripheral arterial disease, lung disease, hip fracture, herniated disc, arthritis, osteoporosis and cognitive deterioration) was calculated. Identification of cardiovascular disease at baseline (including angina pectoris, myocardial infarction, stroke or transient ischemic attack) was

Table 1. Sample characteristics

Characteristic	*N = 900*
Sociodemographics	
Age (years), mean (SD)	74.5 (6.9)
Women, %	54.9
Education (years), mean (SD)	5.4 (3.3)
Health indicators	
Smoking status	
Never, %	57.7
Former, %	27.9
Current, %	14.4
Alcohol intake (≥ 3 drinks a day), %	10.4
Body mass index, mean (SD)	27.4 (4.0)
Waist circumference (cm), mean (SD)	92.6 (10.3)
Systolic blood pressure (mmHg), mean (SD)	150 (19.3)
Depressive symptoms (CES-D), mean (SD)	12.7 (8.6)
Cognitive functioning (MMSE), median (IQR)	26 [23-28]
Number of chronic diseases, mean (SD)	1.3 (1.0)
Baseline cardiovascular disease, mean (SD)	13.6
Cortisol	
Severe renal function impairment, %	2.4
Corticosteroid use, %	1.9
Urine volume (ml), mean (SD)	1508 (569)
24-h Urinary cortisol (µg), mean (SD)	97.9 (48.2)
Mortality	
Deceased, %	23.0
Non-cardiovascular death, %	17.8
Cardiovascular death, %	5.2

CES-D = Center for Epidemiologic Studies Depression scale; MMSE = Mini-Mental State Exam

based on a standardized algorithm using information on self-reported history, pharmacological treatments, medical exam data, and hospital discharge records.[22] Further, some variables that might profoundly affect urinary cortisol levels were considered. Serum creatinine, measured through a modified Jaffe method, was used to calculate creatinine clearance with the Cockcroft-Gault formula. Following K/DOQI guidelines,[23] a creatinine clearance rate of 30 ml/min or lower was considered to indicate severe renal function impairment. Drugs taken in the previous two weeks were identified and coded according to the World Health Organization Anatomical Therapeutic Chemical classification to ascertain use of corticosteroids (code H02).

Statistical analyses

Descriptive statistics were used to present sample characteristics. Cox regression analyses were performed to assess whether urinary cortisol levels predict the risk of all-cause, non-cardiovascular, and cardiovascular mortality in an age- and sex-adjusted and a fully adjusted (age, sex, education, smoking, alcohol intake, body mass index, waist circumference, systolic blood pressure, depressive symptoms, cognitive functioning, number of chronic diseases, baseline cardiovascular disease, renal failure, corticosteroid use and urine volume) model. The proportional hazards assumption was checked by including a time-to-event by cortisol interaction term. An additional analysis excluded persons with severe renal function impairment and/or corticosteroid use. Next, a baseline cardiovascular disease by cortisol interaction term was included in the above-mentioned model, to test whether associations were consistent across persons with and without pre-existing cardiovascular disease. SPPS 15.0 was used for all statistical analyses. A two-sided p-value of ≤ 0.05 was considered statistically significant.

Results

Sample characteristics are shown in Table 1. Mean age of the current sample was 74.5 (SD = 6.9) years, 54.9% were women and the mean 24-h urinary cortisol level was 97.9 (SD = 48.2) µg. During an average follow-up of 5.7 (SD = 1.3) years, 207 persons deceased (23.0%) of whom 47 (5.2%) died from cardiovascular causes and 160 (17.8%) from other causes. Table 2 shows the results of both sex- and age-adjusted and fully-adjusted Cox regression analyses assessing the association between 24-h urinary cortisol and all-cause, non-cardiovascular, and cardiovascular death. The proportional hazards assumption was met in all analyses. Urinary cortisol was not associated with all-cause or non-cardiovascular mortality, but predicted cardiovascular death. After adjustment for sociodemographics, lifestyle, and health indicators, urinary cortisol tended to be linearly associated with increased risk of cardiovascular mortality (HR per SD increase = 1.27, 95% CI = 0.96-1.67). When examining urinary cortisol tertiles, persons in the highest tertile of urinary cortisol had an almost three times increased risk of dying of cardiovascular disease (HR = 2.92, 95% CI = 1.31-6.50). When excluding persons with severe renal function impairment and/or corticosteroid use (N excluded = 39), associations between urinary cortisol and cardiovascular mortality became somewhat stronger (e.g. highest versus lowest tertile: HR = 3.66, 95% CI = 1.55-8.62, p = .003). Next, a baseline cardiovascular disease by cortisol tertile interaction term was included in this Cox regression model, but was not significant (p = .66). This indicated that the association between urinary cortisol and cardiovascular mortality existed for both persons with and without pre-existing cardiovascular disease. These findings are illustrated in Figure 1. Compared to persons without baseline cardiovascular disease in the lowest tertile of cortisol, those in the highest tertile had a 3.6 times increased risk of dying over 6 years when cardiovascular disease was not present at baseline (HR = 3.61, 95% CI = 1.36-9.62) and a 5.8 times increased risk when cardiovascular disease pre-existed at baseline (HR = 5.82, 95% CI =1.64-20.63).

Table 2. Urinary cortisol and 6-year all-cause and cardiovascular mortality

N = 900	Sex- & age-adjusted [a]			Fully adjusted [b]		
	HR	95%CI	p	HR	95%CI	p
All-cause mortality *(N deaths = 207)*						
24-h Urinary cortisol [c]	1.00	0.87-1.15	.97	1.05	0.91-1.21	.49
Tertiles of 24-h urinary cortisol						
First tertile (< 76 µg)		REF			REF	
Second tertile (76-110 µg)	0.92	0.65-1.31	.64	1.14	0.79-1.64	.49
Third tertile (> 110 µg)	1.00	0.71-1.40	.98	1.20	0.83-1.73	.33
Non-cardiovascular mortality *(N deaths = 160)*						
24-h Urinary cortisol [c]	0.94	0.79-1.11	.43	0.99	0.84-1.16	.86
Tertiles of 24-h urinary cortisol						
First tertile (< 76 µg)		REF			REF	
Second tertile (77-110 µg)	0.78	0.53-1.16	.22	0.96	0.63-1.42	.83
Third tertile (> 110 µg)	0.78	0.53-1.15	.21	0.92	0.61-1.41	.71
Cardiovascular mortality *(N deaths = 47)*						
24-h Urinary cortisol [c]	1.23	0.95-1.59	.12	1.27	0.97-1.67	.09
Tertiles of 24-h urinary cortisol						
First tertile (< 76 µg)		REF			REF	
Second tertile (77-110 µg)	1.69	0.78-3.69	.19	2.13	0.95-4.77	.07
Third tertile (> 110 µg)	2.26	1.10-4.65	.03	2.93	1.31-6.50	.009

[a] Based on Cox regression analyses adjusted for sex and age; [b] additionally adjusted for education, smoking status, alcohol intake, body mass index, waist circumference, systolic blood pressure, depressive symptoms, cognitive functioning, number of chronic diseases, baseline cardiovascular disease, renal failure, corticosteroid use and urine volume; [c] HR per SD (= 48 µg) increase.

Discussion

The results of this study show that basal cortisol levels in a general older population predict cardiovascular death, but not all-cause mortality. Persons in the highest tertile of urinary cortisol had a three-fold increased risk of dying of cardiovascular disease over a 6-year period. This finding supports the frequently hypothesized link between hyperactivity of the HPA-axis and cardiovascular disease.

The HPA-axis controls a set of neuroendocrine reactions essential to life. When the HPA-axis is activated, corticotrophin releasing hormone (CRH) is released by the hypothalamus and stimulates the pituitary to release adrenocorticotrophic hormone (ACTH), which in turn signals to the adrenal cortex to release cortisol. Cortisol, in turn, exerts negative feedback on the pituitary and hypothalamus to suppress ACTH and CRH production, respectively.[2] This implies that hyperactivity of the HPA-axis could be the result

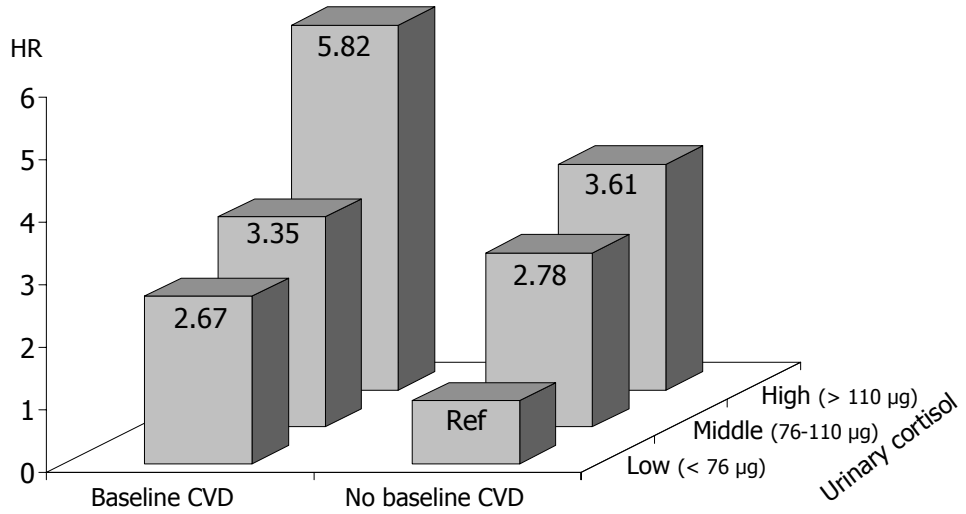

Figure 1. Risk [a] of cardiovascular mortality across baseline cardiovascular disease and urinary cortisol

CVD = cardiovascular disease. [a] Based on Cox regression analyses adjusted for sex, age, education, smoking status, alcohol intake, body mass index, waist circumference, systolic blood pressure, depressive symptoms, cognitive functioning, number of chronic diseases, renal failure, corticosteroid use and urine volume.

of either a CRH overdrive, a strong ACTH response to CRH, a strong cortisol response to ACTH and/or blunted negative feedback exerted by cortisol on central glucocorticoid receptors.[24] It has been hypothesized that hyperactivity of the HPA-axis may be a result of frequent or persistent stimulation.[11] In particular, hyperactivity of the HPA axis has been found as a result of chronic stress,[25] and is suggested to play a role in stress-related disorders such as depression.[26] In addition, aging is associated with an increase in basal cortisol levels[27,28] and an increased cortisol response to challenge.[29] Hyperactivity of the HPA-axis in aging might in fact be the result of the 'wear and tear' of a lifelong exposure to stress.[27]

Hyperactivity of the HPA-axis might exert damage to the human body in the long-run. High levels of cortisol have been associated with several cardiovascular risk factors, such as present in the metabolic syndrome and atherosclerosis.[5-9] As cortisol exerts a multitude of effects on glucose and free fatty acids metabolism, the autonomic nervous system, the inflammatory system, and on sex and growth hormones,[1-4] it is not surprising that continuous high levels of cortisol might lead to dysfunctioning of these systems which are all implicated in cardiovascular disease.[3,10,30] For instance, by activating lipoprotein lipase and inhibiting lipid mobilization, cortisol promotes the accumulation of visceral fat,[1] as visceral fat is highly sensitive to cortisol owing to a high density of glucocorticoid receptors.[31] Visceral fat, in turn, has been shown to be an important risk factor for cardiovascular

disease.[32,33] Also, hyperactivity of the HPA-axis has been linked to the decline of immune functions during aging, particularly among chronically stressed older persons.[34] This, again, may put persons at increased risk of cardiovascular disease.[30]

Thus, research has demonstrated cortisol to be associated with cardiovascular risk factors, however, little prospective evidence exists that cortisol actually predicts the onset of cardiovascular end-points. One previous study in the general population among middle-aged men found that a cortisol/testosterone ratio was predictive of incident ischemic heart disease over 16.5 years of follow-up.[16] No effects of either cortisol or testosterone alone were found. This study used a less reliable single measure of morning cortisol in blood which, unlike urinary or salivary cortisol, does not represent the biological active cortisol and could possibly be increased by an acute stress reaction due to the blood draw itself. Our study, within an older general population confirms that persons with high basal levels of cortisol are indeed at an increased risk of cardiovascular death.

A few studies within heart patients have previously shown that cortisol predicts subsequent events or mortality.[12-14] However, as these persons already have disease at time of cortisol assessment it is hard to disentangle whether cortisol is a cause or a consequence of disease status. The results of our study show that urinary cortisol predicted cardiovascular mortality in both persons with and without cardiovascular disease at baseline. This suggests that high cortisol levels are not merely a reflection of heart disease severity and might have a direct causal effect on cardiovascular death. On the other hand, it is possible that among those without pre-existing cardiovascular disease, those with higher cortisol did have worse health status. However, we adjusted for several health indicators and this only strengthened the association between cortisol and cardiovascular disease.

We found that cortisol was associated with cardiovascular, but not non-cardiovascular mortality. This indicates that the HPA-axis might have specifically damaging effects on the cardiovascular system, and has less profound consequences on other vital physiological systems. In contrast, another recent study in an older general population by Schoorlemmer et al.[18] did find salivary cortisol, but not serum cortisol, to be predictive of all-cause mortality over 7 years of follow-up. This study was not able to differentiate between causes of death. Therefore, it is possible that the association of cortisol was only restricted to those with cardiovascular deaths and not non-cardiovascular deaths, as in our study. The study by Schoorlemmer et al., however, did not find an association between cortisol and the onset of nonfatal heart disease. As heart disease was only measured by self-report, misclassification could have prevented the authors detecting any association between cortisol and heart disease. On the other hand, it is possible that when cortisol levels are increased a cardiac event is more likely to result in death, which is corroborated by the finding that high cortisol levels in heart patients seem to predict mortality.[12-14]

Strengths of the present study include the use of urinary cortisol, which represents the biological active cortisol and can be non-stressfully measured. Furthermore, we were able to examine the effects of cortisol on all-cause and cardiovascular mortality in a large randomly selected sample of the general older population including persons with and without cardiovascular disease. Limitation of this study is that despite the large sample size, there were rather few cases of cardiovascular death. The fact that we only found a trend of

association of continuous urinary cortisol levels with cardiovascular death may have been a result of this. Nevertheless, even with this relatively small number of cases, strong clinically relevant significant effects of high urinary cortisol levels on cardiovascular mortality were found, indicating that a threshold effect, rather than a linear effect may exist.

In conclusion, high cortisol levels in older persons predict cardiovascular death among both persons with and without pre-existing cardiovascular disease. The specific link with cardiovascular - and not all-cause - mortality suggests that hyperactivity of the HPA-axis might be particularly damaging to the cardiovascular system.

Acknowledgements

The InCHIANTI study was supported as a targeted project (ICS 110.1/RS97.71) by the Italian Ministry of Health and in part by the US National Institute on Aging (263 MD 916413 and 263 MD 821336). Data analyses were supported through grant 1R01-HL972972 from the National Heart, Lung and Blood Institute. Cortisol assays were supported by a professional services contract from the Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging.

References

1. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev.* 2001;2:73-86.
2. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992;267:1244-1252.
3. Whitworth JA, Williamson PM, Mangos G, Kelly JJ. Cardiovascular consequences of cortisol excess. *Vasc Health Risk Manag.* 2005;1:291-299.
4. Franchimont D, Kino T, Galon J, Meduri GU, Chrousos G. Glucocorticoids and inflammation revisited: the state of the art. NIH clinical staff conference. *Neuroimmunomodulation.* 2002;10:247-260.
5. Brunner EJ, Hemingway H, Walker BR et al. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. *Circulation.* 2002;106:2659-2665.
6. Fraser R, Ingram MC, Anderson NH, Morrison C, Davies E, Connell JM. Cortisol effects on body mass, blood pressure, and cholesterol in the general population. *Hypertension.* 1999;33:1364-1368.
7. Vogelzangs N, Suthers K, Ferrucci L et al. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. *Psychoneuroendocrinology.* 2007;32:151-159.
8. Dekker MJ, Koper JW, van Aken MO et al. Salivary cortisol is related to atherosclerosis of carotid arteries. *J Clin Endocrinol Metab.* 2008;93:3741-3747.
9. Matthews K, Schwartz J, Cohen S, Seeman T. Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosom Med.* 2006;68:657-661.
10. Bjorntorp P. Heart and soul: stress and the metabolic syndrome. *Scand Cardiovasc J.* 2001;35:172-177.
11. Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. *Psychoneuroendocrinology.* 2005;30:1-10.
12. Guder G, Bauersachs J, Frantz S et al. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. *Circulation.* 2007;115:1754-1761.
13. Marklund N, Peltonen M, Nilsson TK, Olsson T. Low and high circulating cortisol levels predict mortality and cognitive dysfunction early after stroke. *J Intern Med.* 2004;256:15-21.
14. Tenerz A, Nilsson G, Forberg R et al. Basal glucometabolic status has an impact on long-term prognosis following an acute myocardial infarction in non-diabetic patients. *J Intern Med.* 2003;254:494-503.
15. Rotman-Pikielny P, Roash V, Chen O, Limor R, Stern N, Gur HG. Serum cortisol levels in patients admitted to the department of medicine: Prognostic correlations and effects of age, infection, and comorbidity. *Am J Med Sci.* 2006;332:61-67.

16. Smith GD, Ben-Shlomo Y, Beswick A, Yarnell J, Lightman S, Elwood P. Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. *Circulation.* 2005;112:332-340.
17. Boscarino JA. Psychobiologic predictors of disease mortality after psychological trauma: implications for research and clinical surveillance. *J Nerv Ment Dis.* 2008;196:100-107.
18. Schoorlemmer RM, Peeters GM, van Schoor NM, Lips P. Relationships between cortisol level, mortality and chronic diseases in older persons. *Clin Endocrinol (Oxf).* 2009;71:779-786.
19. Ferrucci L, Bandinelli S, Benvenuti E et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc.* 2000;48:1618-1625.
20. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.
21. Folstein M, Folstein S, McHugh P. Mini-mental state: a practical method for grading the state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.
22. Guralnik JM, Fried LP, Simonsick EM, Kasper JD, Lafferty ME. *The Women's Health and Aging Study. Health and Social Characteristics of Older Women with Disability*. Bethesda, MD: National Institute on Aging; NIH Publication No. 95-4009; 1995.
23. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1-266.
24. Pasquali R, Vicennati V. Activity of the hypothalamic-pituitary-adrenal axis in different obesity phenotypes. *Int J Obes Relat Metab Disord.* 2000;24 Suppl 2:S47-S49.
25. Lightman SL. The neuroendocrinology of stress: a never ending story. *J Neuroendocrinol.* 2008;20:880-884.
26. Vreeburg SA, Hoogendijk WJ, van Pelt J et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry.* 2009;66:617-626.
27. Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab.* 1996;81:2468-2473.
28. Veldhuis JD, Keenan DM, Roelfsema F, Iranmanesh A. Aging-related adaptations in the corticotropic axis: modulation by gender. *Endocrinol Metab Clin North Am.* 2005;34:993-9xi.
29. Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology.* 2005;30:80-91.
30. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation.* 2004;109:II2-10.
31. Bronnegard M, Arner P, Hellstrom L, Akner G, Gustafsson JA. Glucocorticoid receptor messenger ribonucleic acid in different regions of human adipose tissue. *Endocrinology.* 1990;127:1689-1696.
32. Gelber RP, Gaziano JM, Orav EJ, Manson JE, Buring JE, Kurth T. Measures of obesity and cardiovascular risk among men and women. *J Am Coll Cardiol.* 2008;52:605-615.
33. Nicklas BJ, Penninx BWJH, Cesari M et al. Association of visceral adipose tissue with incident myocardial infarction in older men and women: the Health, Aging and Body Composition Study. *Am J Epidemiol.* 2004;160:741-749.
34. Bauer ME, Jeckel CM, Luz C. The role of stress factors during aging of the immune system. *Ann N Y Acad Sci.* 2009;1153:139-152.

Chapter 9

Cardiovascular disease in persons with depressive and anxiety disorders

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Journal of Affective Disorders 2010; in press.

Abstract

Background

Associations between depression, and possibly anxiety, with cardiovascular disease have been established in the general population and among heart patients. This study examined whether cardiovascular disease was more prevalent among a large cohort of depressed and/or anxious persons. In addition, the role of specific clinical characteristics of depressive and anxiety disorders in the association with cardiovascular disease was explored.

Methods

Baseline data from the Netherlands Study of Depression and Anxiety were used, including persons with a current (i.e. past year) or remitted DSM-IV depressive or anxiety disorder (N = 2315) and healthy controls (N = 492). Additional clinical characteristics (subtype, duration, severity, and psychoactive medication) were assessed. Cardiovascular disease (stroke and coronary heart disease) was assessed using algorithms based on self-report and medication use.

Results

Persons with current anxiety disorders showed an about three-fold increased prevalence of coronary heart disease (OR anxiety only = 2.70, 95% CI = 1.31-5.56; OR comorbid anxiety/depression = 3.54, 95% CI = 1.79-6.98). No associations were found for persons with depressive disorders only or remitted disorders, nor for stroke. Severity of depressive and anxiety symptoms - but no other clinical characteristics - most strongly indicated increased prevalence of coronary heart disease.

Limitations

Cross-sectional design.

Conclusions

Within this large psychopathology-based cohort study, prevalence of coronary heart disease was especially increased among persons with anxiety disorders. Increased prevalence of coronary heart disease among depressed persons was largely owing to comorbid anxiety. Anxiety - alone as well as comorbid to depressive disorders - as risk indicator of coronary heart disease deserves more attention in both research and clinical practice.

Introduction

In 1993 Frasure-Smith et al.[1] showed that after a myocardial infarction, depressed persons were four-to-five times as likely to die within the next six months than their non-depressed counterparts. Although this initial observation turned out to overestimate the true relationship between depression and heart disease,[2] since then, many studies have examined their association. Both depression and heart disease are leading disorders when considering disease burden. The World Health Organization projected depression and heart disease to become number 1 and 2, respectively, on the list of diseases with the greatest loss of 'disability adjusted life years' in 2030 in high-income countries and number 2 and 3 worldwide.[3] This suggests an enormous possible gain in public health and disease burden when depression, heart disease and especially their comorbidity could be prevented through increasing knowledge on the link between these two disabling diseases.

Research thus far has mainly focused on two kinds of populations: heart disease patients and the general population. Meta-analyses have shown that among heart patients depression is associated with an 1.8 to 2.6 increased risk of a subsequent cardiovascular event or death,[2,4,5] while in the general population depression increases risk of cardiovascular disease (CVD) about 1.6 to 1.8 times.[2,6-8] Although, as suggested by Nicholson et al.,[2] these estimates may still be inflated due to incomplete and biased reporting of adjustment for conventional risk factors and CVD severity. Studies on prevalence of CVD within a psychopathology-based population are largely lacking. From a psychiatrist perspective, it would be of great importance to know whether clinically depressed patients indeed have a higher prevalence of CVD and how much increased exactly this prevalence is. What's more, it has hardly been addressed whether specific characteristics of depression, such as age of onset, duration, or severity of the disorder could further determine the exact CVD probability, or whether the association is restricted to specific subtypes, such as atypical or melancholic depression. This knowledge could give insight into underlying mechanisms that relate depression and CVD as well as into which patients should be most closely monitored for cardiovascular dysfunctioning.

Besides depression, some studies have suggested anxiety to be associated with CVD as well.[9-11] Anxiety disorders lead to comparable levels of disability as depression and heart disease[12] and have been found to increase risk of premature all-cause and cardiovascular death.[13,14] The association between anxiety and CVD, however, has been far less studied than the link between depression and heart disease. Even less studied has been the association between anxiety characteristics (subtype, duration, and severity) and CVD. Furthermore, as depression and anxiety are often found to be co-morbid, it would be of great importance to study the association between depression and anxiety with CVD in concert. This could shed light on the specificity of associations between depressive and anxiety disorders and CVD.

Therefore, in the present study within a large cohort of depressed and/or anxious persons and healthy controls we examined the (extent of the) association between the presence of a psychiatric diagnosis of depressive and/or anxiety disorder with CVD. In addition, we assessed the specificity of these associations by directly comparing depressive with anxiety disorders and by examining whether specific characteristics of depressive

and/or anxiety disorders (subtype, duration, severity, and psychoactive medication) could be identified that indicate increased probability of CVD.

Methods

Sample

The Netherlands Study of Depression and Anxiety (NESDA) is an ongoing cohort study designed to investigate the long-term course and consequences of depressive and anxiety disorders. Participants were 18 to 65 years old at baseline assessment in 2004-2007 and were recruited from the community (19%), general practice (54%) and secondary mental health care (27%). A total of 2981 persons were included, consisting of persons with a current or past depressive and/or anxiety disorder (N = 2329) and healthy controls (N = 652). A detailed description of the NESDA study design and sampling procedures can be found elsewhere.[15] The research protocol was approved by the Ethical Committee of participating universities and after complete description of the study all respondents provided written informed consent.

As subclinical symptoms of on the one hand depressive and anxiety disorders and on the other hand CVD could to a certain degree resemble each other (e.g. feeling tired or pain on the chest) and could therefore falsely indicate or elevate an association between them, persons with subthreshold symptoms of depression or anxiety but no formal diagnosis of depressive or anxiety disorder (N = 158) and persons who self-reported CVD without reporting accompanying appropriate medication use (N = 16) were excluded (see below for more details), leaving 2807 persons for the present analyses.

Psychopathology and clinical characteristics

Presence of depressive disorder (major depressive disorder and dysthymia) and anxiety disorder (social phobia, generalized anxiety disorder, panic disorder and agoraphobia) was established using the Composite Interview Diagnostic Instrument (CIDI) according to DSM-IV criteria.[16] The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders[17] and was administered by specially trained research staff. Based on CIDI, participants were categorized as having no, current (i.e. in past year), or a remitted (lifetime, but not current) depressive and/or anxiety disorder. In addition, a categorical variable was constructed classifying persons as having no depressive or anxiety disorder, remitted depressive or anxiety disorder, current depressive disorder only, current anxiety disorder only, or current depressive and anxiety disorder.

Clinical characteristics examined included the subtype, duration and severity of the depressive or anxiety disorder. Next to CIDI diagnoses, subtypes of depressive disorder included first onset versus recurrent major depressive disorder (based on CIDI interview), presence of an atypical symptom profile, and presence of a melancholic symptom profile. Atypical symptom profile (mood reactivity and ≥ 2 of hyperphagia, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity) was constructed by comparison of items of the 28-item self-report Inventory of Depressive Symptoms (IDS)[18] with DSM-IV criteria for atypical depression following Novick's algorithm.[19] Similarly, melancholic symptom profile (lack of mood reactivity or loss of pleasure and ≥ 3 of distinct mood quality, mood worse in

morning, early morning awakening, psychomotor retardation or agitation, anorexia/weight loss, and guilt feelings) was constructed based on comparison of IDS items with DSM-IV criteria using the algorithm proposed by Khan.[20] Additionally, for both depressive and anxiety disorders a distinction was made between late onset (≥ 30 years old) and early onset (< 30 years old) of the psychiatric disorder, as derived from the CIDI interview. Using the Life Chart method,[21] a detailed account of the presence of depressive and anxiety symptoms during the past four to five years was assessed among persons with depressive or anxiety disorders. From this, the percent of time patients reported depressive or anxiety symptoms was computed as a measure of duration. Severity of depressive symptoms was assessed by means of the IDS; severity of anxiety symptoms by means of the 21-item Beck Anxiety Inventory (BAI).[22]

To account for possible psychoactive medication effects, medication use was assessed based on drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification.[23] As effects of psychoactive medication are likely negligible when used infrequently, use of psychoactive medication was only considered present when taken on a regular basis (at least 50% of the time). Antidepressants included selective serotonin reuptake inhibitors (ATC-code N06AB), tricyclic antidepressants (N06AA) and other antidepressants (N06AF/N06AX). Benzodiazepines included ATC-codes N03AE, N05BA, N05CD and N05CF.

Cardiovascular disease

Cardiovascular disease (CVD) included stroke, angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting and was adjudicated using standardized algorithms considering self-report and medication use (based on drug container inspection and ATC coding). During the interview, participants were asked if they ever had a stroke, a heart condition or a heart attack, and to specify the kind of condition. In addition, it was asked whether subjects were ever troubled by chest pain during physical strain and whether the pain disappeared within 10 min after standing still or taking a tablet under the tongue. If subjects responded positively on both questions this was regarded as an indication of angina pectoris (symptoms). Stroke was identified by self-report supported by use of either anticoagulant/antiplatelet agents (antithrombotic agents [ATC-code B01], acetylsalicylic acid [N02BA01; ≥ 50% use of ≤ 100 mg], or carbasalate calcium [N02BA15]), any medication for hypertension (antihypertensives [C02], diuretics [C03], beta blocking agents [C07], calcium channel blockers [C08], agents acting on renin-angiotensin system [C09]), or lipid modifying agents (C10). Angina pectoris and myocardial infarction were only considered present when self-report (or symptoms) of the disease was supported by use of medication for coronary heart disease (CHD; beta blocking agents [C07], nitrate vasodilators [C01DA], calcium channel blockers [C08], or anticoagulant/antiplatelet agents [B01, N02BA01 ≥ 50% use of ≤100 mg, N02BA15]). When self-report was not confirmed by medication use, CVD was considered to be 'undetermined' and subjects were excluded from the analyses (N = 16). When angina *symptoms* (N = 510) were not supported by medication use, persons were considered as having no CVD (N =

413). Percutaneous transluminal coronary angioplasty and coronary artery bypass grafting were based on self-report only. CVD was subdivided into stroke and CHD (angina pectoris, myocardial infarction, angioplasty or bypass). For sensitivity analyses, as beta blockers are sometimes prescribed for anxiety symptoms, a secondary measure of CHD excluded persons with symptoms of angina pectoris and use of a beta blocker only (N excluded = 32).

Covariates

Sociodemographic characteristics included age, sex, and years of education. As lifestyle characteristics can be associated with both CVD and depression/anxiety, smoking status (never, former, current), alcohol intake (< 1, 1-14, > 14 drinks per week), physical activity (measured with the International Physical Activity Questionnaire[24] in MET-minutes [ratio of energy expenditure during activity compared to rest times the number of minutes performing the activity] per week) and body mass index (BMI; weight in kilograms divided by height in meters squared) were assessed.

Statistical analyses

Sample characteristics were compared across persons with and without CVD using independent t tests for continuous variables and X^2 tests for dichotomous and categorical variables. Logistic regression analyses assessed the association with CVD for depressive and anxiety disorders separately and simultaneously, before and after adjustment for a priori selected covariates (sociodemographic [age, sex, years of education] and lifestyle [smoking status, alcohol intake, physical activity, BMI]). Next, consistency of associations with regard to CVD were assessed by conducting separate adjusted logistic regression analyses for subtypes of CVD (stroke and CHD) and subtypes of CHD (angina pectoris, myocardial infarction, and CHD surgery [angioplasty or bypass]).

Specificity of associations with regard to clinical aspects of the depressive or anxiety disorder was assessed in a sub-sample of persons with current depressive and/or anxiety disorders using sociodemographic-adjusted logistic regression analyses. First, the association with CVD of depressive disorder versus anxiety disorder was directly compared. Second, associations between specific depressive disorder or anxiety disorder characteristics (subtype, duration, severity, and psychoactive medication use) and CVD were examined.

Results

Mean age of the present sample was 41.8 (SD = 13.0) years, 66.4% were women, 19.4% had a remitted and 63.1% had a current depressive or anxiety disorder, while 5.6% had CVD. Table 1 describes sample characteristics comparing persons with and without CVD. Persons with CVD were older, more often men, less educated, more often former smoker, less often moderate drinker, and had a higher BMI. Also, persons with CVD more often had a current anxiety disorder, but not depressive disorder.

Table 2 describes the results of unadjusted and adjusted logistic regression analyses assessing the association of depressive and anxiety disorders with CVD. Remitted disorders were not statistically significantly associated with CVD, but after adjustment current depressive and current anxiety disorders were (OR = 1.59, 95% CI = 1.02-2.47; OR = 2.18,

Table 1. Sample characteristics by cardiovascular disease status

Characteristic	***No CVD*** *N = 2651*	***CVD*** *N = 156*	p [a]
Sociodemographic variables			
Age, years, mean (SD)	41.1 (12.9)	54.1 (7.8)	<.001
Women, %	67.7	45.5	<.001
Years of education, mean (SD)	12.2 (3.3)	11.0 (3.2)	<.001
Lifestyle variables			
Smoking status			.001
Never, %	28.4	18.6	
Former, %	32.3	46.2	
Current, %	39.3	35.3	
Alcohol intake			.05
< 1 Drink a week, %	32.2	37.8	
1-14 Drinks a week, %	52.1	42.3	
> 14 Drinks a week, %	15.7	19.9	
Physical activity (in MET-minutes/week), mean (SD)	3720 (3046)	3423 (3198)	.24
Body mass index, mean (SD)	25.4 (5.0)	28.6 (4.8)	<.001
Depression and anxiety variables			
Depressive disorder			.14
No depressive disorder, %	30.6	23.7	
Remitted depressive disorder, %	24.4	29.5	
Current (in past year) depressive disorder, %	45.0	46.8	
Anxiety disorder			.007
No anxiety disorder, %	37.9	26.3	
Remitted anxiety disorder, %	14.6	14.1	
Current (in past year) anxiety disorder, %	47.5	59.6	
Depressive and/or anxiety disorder			.03
No depressive or anxiety disorder	17.8	12.2	
Remitted depressive or anxiety disorder	19.4	19.2	
Current depressive disorder only	15.2	9.0	
Current anxiety disorder only	17.7	21.8	
Current depressive and anxiety disorder	29.8	37.8	

[a] Based on independent t-test for continuous variables and X^2 tests for dichotomous and categorical variables.

Table 2. Association [a] of depressive and anxiety disorders with cardiovascular disease

		Unadjusted			Adjusted		
Psychiatric disorder status	N	OR	95% CI	p	OR	95% CI	p
Depressive disorder							
No depressive disorder	847		REF			REF	
Remitted depressive disorder	693	1.56	1.00-2.43	.05	1.50	0.93-2.40	.10
Current (in past year) depressive disorder	1267	1.34	0.89-2.01	.16	1.59	1.02-2.47	.04
Anxiety disorder							
No anxiety disorder	1046		REF			REF	
Remitted anxiety disorder	408	1.40	0.82-2.38	.22	1.31	0.74-2.30	.35
Current (in past year) anxiety disorder	1353	1.81	1.24-2.64	.002	2.18	1.45-3.28	<.001
Depressive and/or anxiety disorder							
No depressive or anxiety disorder	492		REF			REF	
Remitted depressive or anxiety disorder	544	1.45	0.81-2.62	.21	1.27	0.68-2.37	.45
Current depressive disorder only	418	0.86	0.43-1.74	.68	0.93	0.44-1.96	.85
Current anxiety disorder only	504	1.80	1.01-3.20	.05	1.96	1.06-3.64	.03
Current depressive and anxiety disorder	849	1.86	1.10-3.16	.02	2.35	1.33-4.20	.004

[a] Based on logistic regression analyses unadjusted and adjusted for age, sex, years of education, smoking status, alcohol intake, physical activity and body mass index.

95% CI = 1.45-3.28, respectively). When the presence or absence of a depressive or anxiety disorder was combined in one categorical variable, odds of CVD were increased for persons with a current anxiety disorder alone (OR = 1.96, 95% CI = 1.06-3.64) as well as for those with a combined current anxiety and depressive disorder (OR = 2.35, 95% CI = 1.33-4.20) compared to healthy controls. Increased likelihood of CVD was not observed for persons with a current depressive disorder only (OR = 0.93, 95% CI = 0.44-1.96).

Next, effects of depression/anxiety status were assessed separately for odds of having stroke and odds of having CHD (Table 3). Depressive and anxiety disorders were not associated with stroke. In contrast, persons with a current anxiety disorder were 2.5 to 3.5 times more likely to have CHD (OR anxiety only = 2.70, 95% CI = 1.31-5.56; OR anxiety and depression = 3.54, 95% CI = 1.79-6.98). No significant association was found for persons with a depressive disorder only (OR = 1.41, 95% CI = 0.61-3.23). To gain some insight into the direction of the association between psychopathology and CHD, we repeated the current analysis among persons with an early onset (≤ 30 years) of depressive or anxiety disorder (N excluded = 269). Since CHD hardly occurs before the age of 30, an early onset suggests that psychopathology was present before CHD. Within persons with an early onset of depressive or anxiety disorder similar results were found (OR depression only = 1.37, 95% CI = 0.59-3.20; OR anxiety only = 2.37, 95% CI = 1.12-5.03; OR anxiety and depression = 3.26, 95% CI = 1.59-6.68; data not tabulated). An additional analysis excluded persons (N = 32) who 'earned' their status of CHD only based on angina

Table 3. Association [a] of depressive and anxiety disorders with cardiovascular disease subtypes

	Cardiovascular disease subtypes *(N = 156)*					
	Stroke *(N = 36)*			***Coronary heart disease*** *(N = 133)*		
Psychiatric disorder status	OR	95% CI	p	OR	95% CI	p
No depressive or anxiety disorder		REF			REF	
Remitted depressive or anxiety disorder	0.73	0.24-2.19	.57	1.65	0.79-3.43	.18
Current depressive disorder only	0.53	0.13-2.18	.38	1.41	0.61-3.23	.42
Current anxiety disorder only	1.02	0.34-3.11	.97	2.70	1.31-5.56	.007
Current depressive and anxiety disorder	1.37	0.49-3.86	.55	3.54	1.79-6.98	<.001

	Coronary heart disease subtypes *(N = 138)*								
	Angina pectoris *(N = 105)*			***Myocardial infarction*** *(N = 50)*			***CHD surgery*** *(N = 48)*		
Psychiatric disorder status	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
No depressive or anxiety disorder		REF			REF			REF	
Remitted depressive or anxiety disorder	2.17	0.88-5.34	.09	2.55	0.78-8.40	.12	1.44	0.49-4.24	.50
Current depressive disorder only	2.16	0.82-5.71	.12	2.58	0.70-9.46	.15	1.60	0.50-5.10	.42
Current anxiety disorder only	2.87	1.16-7.11	.02	3.47	1.03-11.66	.05	2.69	0.94-7.67	.06
Current depressive and anxiety disorder	4.96	2.14-11.49	<.001	4.75	1.46-15.47	.01	2.24	0.79-6.37	.13

CHD = coronary heart disease. [a] Based on logistic regression analyses adjusted for age, sex, years of education, smoking status, alcohol intake, physical activity and body mass index; in all analyses the specific cardiovascular disease or coronary heart disease subtype was compared to persons without any cardiovascular disease (N = 2651).

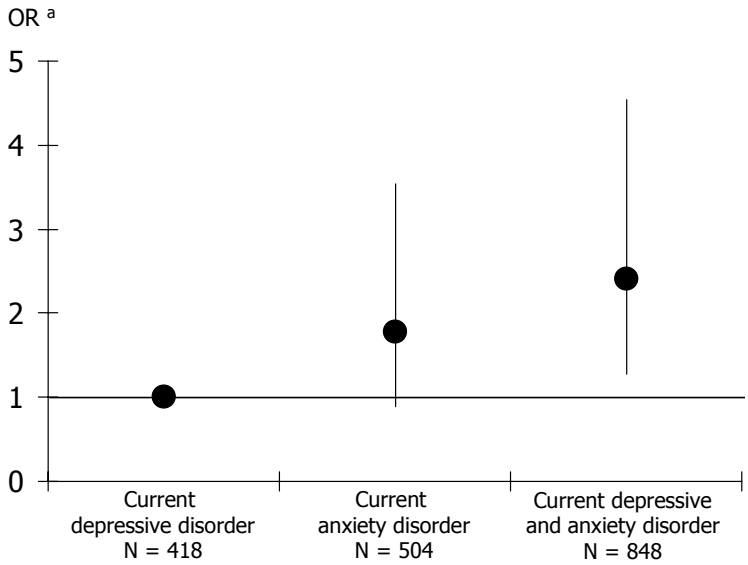

Figure 1. OR for coronary heart disease in persons with a current depressive and/or anxiety disorder.

[a] Based on logistic regression analysis adjusted for age, sex, and education.

Table 4. Association of depressive and anxiety disorder characteristics with coronary heart disease

	No CHD *N = 1673*	***CHD*** *N = 97*			
	% or mean (SD)	% or mean (SD)	OR	95% CI	p
Psychiatric characteristic	Unadjusted		Adjusted [a]		
Type of depressive disorder [b]					
First onset major depressive disorder (vs. recurrent)	46.4	41.8	0.95	0.56-1.61	.85
Atypical symptoms	20.8	24.2	1.53	0.83-2.83	.17
Melancholic symptoms	11.9	16.7	1.08	0.53-2.18	.84
Late onset (≥ 30 years old)	35.0	61.8	1.11	0.65-1.92	.70
Type of anxiety disorder [c]					
Generalized anxiety disorder	44.9	50.0	1.15	0.72-1.82	.56
Social phobia	55.5	53.6	1.08	0.68-1.72	.74
Panic disorder	55.1	53.6	1.13	0.71-1.80	.62
Agoraphobia	16.0	25.0	1.21	0.70-2.10	.49
Late onset (≥ 30 years old)	22.6	43.4	1.06	0.65-1.73	.83
Duration [d]					
Percent of time with symptoms in past 4 years	52.4 (35.6)	58.8 (35.3)	1.02	0.56-1.86	.95
Severity [d]					
Current depressive symptoms score (IDS)	28.5 (12.4)	32.2 (13.0)	1.32 [e]	1.05-1.65	.02
Current anxiety symptoms score (BAI)	16.5 (10.8)	20.0 (9.7)	1.36 [e]	1.11-1.66	.003
Psychoactive medication [d]					
Selective serotonin reuptake inhibitor use	25.1	21.6	0.87	0.52-1.45	.60
Tricyclic antidepressant use	3.8	7.2	1.56	0.68-3.57	.30
Other antidepressant use	8.8	12.4	1.26	0.65-2.41	.49
Benzodiazepine use	10.5	22.7	1.60	0.95-2.71	.08

CHD = coronary heart disease. [a] Based on logistic regression analyses adjusted for age, sex, and education; each line represents a single analysis; [b] within sub-sample of persons with a current (past year) depressive disorder: N = 1266; first onset vs. recurrent: persons with dysthymia only (N = 44) were excluded; [c] within sub-sample of persons with a current (past year) anxiety disorder: N = 1352; [d] within sub-sample of persons with a current (past year) depressive and/or anxiety disorder: N = 1770; [e] per SD increase: IDS: SD = 12.9; BAI: SD = 10.7.

symptoms and use of a beta blocker - sometime used to relieve anxiety symptoms - but substantial associations remained (OR anxiety only = 2.06, 95% CI = 0.96-4.44; OR anxiety and depression = 2.89, 95% CI = 1.41-5.93; data not tabulated). When examining CHD subtypes (angina pectoris, myocardial infarction, and CHD surgery) associations for current anxiety disorder (with or without depressive disorder) were found for all (see Table 3).

Depressive disorders alone also showed increased odds of especially angina pectoris and myocardial infarction, but these were not statistically significant. Because associations of psychopathology were only found with CHD and not stroke, all following analyses were conducted with CHD as the outcome.

Figure 1 shows that within persons with current psychopathology (N = 1770), persons with a current anxiety disorder had almost 80% increased odds to have CHD compared to persons with a current depressive disorder (OR = 1.77, 95% CI = 0.89-3.54), albeit this was not statistically significant. Odds of CHD for persons having an anxiety disorder in addition to a depressive disorder were more than twofold increased compared to having a depressive disorder alone (OR = 2.40, 95% CI = 1.27-4.54).

Table 4 shows the results of separate sociodemographic-adjusted logistic regression analyses examining associations of depressive and anxiety disorder characteristics with CHD in the sub-sample of persons with current psychopathology (N = 1770). No specific subtype of depressive disorder was associated with CHD. For persons with a current anxiety disorder associations with CHD were consistent for persons with generalized anxiety disorder, social phobia, panic disorder and agoraphobia. Duration of depressive or anxious complaints was also not associated with CHD. However, the severity of depressive symptoms (OR per SD increase = 1.32, 95% CI = 1.05-1.65) and of anxiety symptoms (OR per SD increase= 1.36, 95% CI = 1.11-1.66) were significantly associated with CHD. In fact, it appeared that the results from Figure 1 showing a somewhat higher OR in persons with comorbid depression and anxiety in comparison to the OR in persons with anxiety disorders alone could be explained by severity of symptoms. After additional adjustment for severity of depressive and anxiety symptoms, odds of CHD for persons with anxiety disorders were equally increased, irrespective of additional depressive disorder (OR anxiety only = 1.86, 95% CI = 0.91-3.79; OR anxiety and depression = 1.95, 95% CI = 1.00-3.78). Lastly, psychoactive medication use did not statistically significantly increase odds of CHD, but a trend was found for use of benzodiazepines and higher odds of CHD (OR = 1.60, 95% CI = 0.95-2.71). Benzodiazepine use did not affect the before presented results (i.e. ORs of CHD as presented in Table 3 and Figure 1 were very similar after additional adjustment for benzodiazepine use).

Discussion

This study examined the association between diagnosed depressive and anxiety disorders and cardiovascular disease within a large cohort of depressed and/or anxious persons and healthy controls. The results show that, individually, both depressive and anxiety disorders are associated with CVD. However, the increased prevalence of CHD among depressive persons appeared to be mainly owing to comorbidity of anxiety disorders. No associations were found with stroke. Severity of depressive and anxiety symptoms - but no other clinical factors - identified those with the highest prevalence of CHD.

Relatively few studies have examined the link between anxiety and CHD and most of these studies assessed anxiety symptoms, but not diagnosis. Although the link between anxiety (symptoms) and CHD has been more consistently found in initially CHD-free populations than among heart patients,[25] a recent study[26] showed that both a generalized

anxiety disorder, as well as severity of anxiety symptoms were associated with an increased risk of major adverse cardiac events in patients with stable coronary artery disease. Our results demonstrate that within a psychopathology-based population the prevalence of CHD is increased across a wide range of diagnosed anxiety disorders (social phobia, generalized anxiety disorder, panic disorder and agoraphobia). In fact, persons who suffered from any anxiety disorder in the past year were about three times as likely to have CHD. Given the widespread prevalence of anxiety disorders, these results suggest that the role of anxiety disorders in CHD is important and has been largely overlooked thus far. These findings also suggests that cardiac symptoms in anxiety persons might really indicate heart disease and underdiagnosing heart disease in anxiety patients might be a problem.

The possible overlap in symptoms between anxiety disorders and heart disease could also pose a problem in examining the association between these two. We tried to handle this issue by only including definite cases of anxiety and by confirmation of medication use appropriate for CVD. Even when further excluding persons with symptoms of chest pain and use of a beta-blocker only - sometimes described to relieve anxiety symptoms - associations of anxiety disorders with CHD remained. Moreover, associations between anxiety disorders and CHD were found across different types of both CHD and anxiety disorders and were not confined to for instance angina pectoris and panic disorder, supporting the conclusion that the strong association observed between anxiety and CHD is real.

Although a depressive disorder diagnosis was associated with CVD, this relationship appeared to be largely explained by comorbid anxiety. Previous research in the general population and among heart patients consistently showed an association between depression and CVD. Importantly, these studies often did not take into account comorbid anxiety, but many depressed persons have a co-morbid anxiety disorder (in our sample 67%). Similar to our study within a psychopathology-based population, Strik et al.[27] found that anxiety and not depressive symptoms were an independent predictor of cardiac events among heart patients and accounted for the relationship between depressive symptoms and cardiac events. Longitudinal studies should further disentangle the associations between depression, anxiety and CHD.

Considering clinical characteristics, highest prevalences of CHD were found among those with the most severe symptoms of depression and anxiety. This might suggest that more severe symptoms induce an extra increased risk of CHD. Otherwise, as symptom scales of depression and anxiety often include a set of somatic items, it is possible that severity of depression or anxiety partly reflects severity of heart complaints.[28] Otherwise, somatic health factors might be more important in depressive disorders that are associated with CVD. This might also (partly) explain why other studies, mostly conducted within somewhat older populations, which generally have more somatic conditions, do find more support of a relationship between depression and CVD.

Little evidence was found of other clinical characteristics of depressive or anxiety disorders to be specifically related to CHD. Although we had expected longer lasting psychiatric disorders to be associated with higher prevalence of CVD, the results did not corroborate this. This finding somewhat decreases the plausibility of depressive and anxiety disorders directly causing CVD. Also, associations with remitted psychiatric disorders were

not statistically significant, perhaps partly due to decreased reliability of diagnosis assessment in the more far away past. On a more positive side, this might suggest that when persons remit from depressive or anxiety disorders, the odds of CHD decreases. Further, antidepressant medication use was not associated with CHD. Tricyclic antidepressants have been well described to have cardiovascular effects,[29] but this might have been counterbalanced in our study by the fact that these medications are therefore contra-indicated in heart patients. Benzodiazepine use was somewhat more prevalent among persons with CHD, but whether they increase risk of CVD or whether this finding is a reflection of poorer health status in persons with CVD, cannot be decided from this study.

Interestingly, our results only show an association with CHD, but not with stroke. Although some studies do relate psychopathology to stroke,[30] this has been much less examined than CHD. We examined the association between depression, anxiety and stroke in a relatively young population where stroke was not very prevalent and we were not able to distinguish between ischemic or a hemorrhagic stroke. As an association of depression and anxiety with specifically ischemic stroke is expected, hemorrhagic strokes might have diluted the association.

Our study has some important strengths. We made use of a large sample of persons with diagnosed psychopathology to investigate whether true psychiatric diagnoses of both depression and anxiety are indeed associated with a heightened prevalence of CVD. Furthermore, we were able to examine the effects of a large amount of clinical characteristics of depressive and anxiety disorders. Some limitations have to be noted as well. Our results are based on cross-sectional data. This makes it impossible to draw any conclusions about the causality of associations between depressive and anxiety disorders and CHD. However, a strong association between anxiety disorder and CHD existed in persons with an onset of psychopathology before 30 years. Since CHD hardly occurs before the age of 30, an early onset suggests that psychopathology was present before CHD. Additionally, as depression and anxiety are highly comorbid and had an early onset in most persons (only 269 of 2315 had late onset), it is unlikely that the finding that anxiety is more strongly than depression associated with CHD was biased by the cross-sectional design. Another limitation is that the presence of heart disease was not verified by general practice or hospitalization records. However, self-report was confirmed by medication use and previous research has shown good concordance between self-report of heart disease and general practitioners information, with especially little overreporting.[31,32]

In conclusion, our results show that anxiety disorders are more strongly associated with coronary heart disease than depressive disorders and might partly account for the widely reported association between depression and heart disease. The highest prevalence of CHD is found among those with the most severe psychiatric symptoms, such as those persons with comorbid depression and anxiety. Anxiety as possible risk factor for cardiovascular disease needs to be more elaborately investigated in future research, and deserves more attention in clinical care as well.

Acknowledgements

The infrastructure for the NESDA study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organization for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations (VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Institute for Quality of Health Care (IQ Healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands Institute of Mental Health and Addiction (Trimbos). Data analyses were supported by grant R01-HL72972-01 from the National Heart, Lung, and Blood Institute (NHLBI).

References

1. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA.* 1993;270:1819-1825.
2. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J.* 2006;27:2763-2774.
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3:e442.
4. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med.* 2004;66:802-813.
5. van Melle JP, de JP, Spijkerman TA et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med.* 2004;66:814-822.
6. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med.* 2002;23:51-61.
7. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med.* 2003;65:201-210.
8. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry.* 2007;22:613-626.
9. Kawachi I, Colditz GA, Ascherio A et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation.* 1994;89:1992-1997.
10. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation.* 2005;111:480-487.
11. Fan AZ, Strine TW, Jiles R, Mokdad AH. Depression and anxiety associated with cardiovascular disease among persons aged 45 years and older in 38 states of the United States, 2006. *Prev Med.* 2008;46:445-450.
12. Buist-Bouwman MA, de GR, Vollebergh WA, Alonso J, Bruffaerts R, Ormel J. Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. *Acta Psychiatr Scand.* 2006;113:492-500.
13. Denollet J, Maas K, Knottnerus A, Keyzer JJ, Pop VJ. Anxiety predicted premature all-cause and cardiovascular death in a 10-year follow-up of middle-aged women. *J Clin Epidemiol.* 2009;62:452-456.
14. Phillips AC, Batty GD, Gale CR et al. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. *Psychosom Med.* 2009;71:395-403.
15. Penninx BW, Beekman AT, Smit JH et al. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res.* 2008;17:121-140.
16. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, fourth edition*. 4th ed. Washington, DC: American Psychiatric Association; 2001.
17. Wittchen HU. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res.* 1994;28:57-84.

18. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med.* 1996;26:477-486.
19. Novick JS, Stewart JW, Wisniewski SR et al. Clinical and demographic features of atypical depression in outpatients with major depressive disorder: preliminary findings from STAR*D. *J Clin Psychiatry.* 2005;66:1002-1011.
20. Khan AY, Carrithers J, Preskorn SH et al. Clinical and demographic factors associated with DSM-IV melancholic depression. *Ann Clin Psychiatry.* 2006;18:91-98.
21. Lyketsos CG, Nestadt G, Cwi J, Heithoff K, Eaton WW. The life chart interview: A standardized method to describe the course of psychopathology. *International Journal of Methods in Psychiatric Research.* 1994;4:143-155.
22. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol.* 1988;56:893-897.
23. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical Classification. 2007. Geneva, World Health Organization. Ref Type: Report
24. Craig CL, Marshall AL, Sjostrom M et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc.* 2003;35:1381-1395.
25. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychol Bull.* 2005;131:260-300.
26. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry.* 2008;65:62-71.
27. Strik JJ, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J Am Coll Cardiol.* 2003;42:1801-1807.
28. Sorensen C, Brandes A, Hendricks O et al. Psychosocial predictors of depression in patients with acute coronary syndrome. *Acta Psychiatr Scand.* 2005;111:116-124.
29. Glassman AH. Cardiovascular effects of antidepressant drugs: updated. *J Clin Psychiatry.* 1998;59 Suppl 15:13-18.
30. Everson SA, Roberts RE, Goldberg DE, Kaplan GA. Depressive symptoms and increased risk of stroke mortality over a 29-year period. *Arch Intern Med.* 1998;158:1133-1138.
31. Kehoe R, Wu SY, Leske MC, Chylack LT, Jr. Comparing self-reported and physician-reported medical history. *Am J Epidemiol.* 1994;139:813-818.
32. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol.* 1996;49:1407-1417.

Chapter 10

General discussion

The aim of the present thesis was to examine the association between depression and the metabolic syndrome, taking an epidemiological perspective. First, the cross-sectional association between depression and the metabolic syndrome was investigated. Next, a possible role of the hypothalamic-pituitary-adrenal (HPA)-axis herein was considered. Subsequently, the temporal direction of associations between depression and the metabolic syndrome was examined using longitudinal designs. Lastly, a cross-link was made to cardiovascular disease, which is a frequent and debilitating outcome of the metabolic syndrome and has recurrently been associated with depression. In the present chapter, findings from Chapter 2 through 9 will be integratively summarized and discussed within the context of current scientific evidence. In addition, some notes will be given on methodological issues relevant for this thesis and the possible implications for public health and clinical practice will be portrayed. The chapter finishes with a few suggestions for future research and an overall conclusion.

Are depression and the metabolic syndrome associated?

Results from each of the thesis chapters are summarized in Table 1. Cross-sectional examinations in the present thesis are only partly supportive of an association between depression and the metabolic syndrome. In Chapter 2 depressive symptoms were modestly associated with the metabolic syndrome in older white persons, but not in older black persons. In Chapter 3 a significant association was found between depressive symptoms and the metabolic syndrome, mainly due to high cortisol levels among the depressed. In Chapter 4 no significantly increased odds of metabolic syndrome was found for persons with major depressive disorder. Persons with subthreshold depressive symptoms even had a decreased odds of the metabolic syndrome. In the past few years, several other studies have tested the cross-sectional association between depression, almost exclusively assessed by means of symptoms checklists, and the metabolic syndrome.[1-13] Most of these studies, including both smaller and larger sample size studies, and younger and older age samples, found an association between depressive symptoms and the metabolic syndrome.[1-10] Some of these studies observed gender-specific effects, with associations found either only in women[3,8] or only in men.[2,10] In contrast, a small number of large studies,[11-13] including 4000 up to almost 10.000 persons, was not able to show an association between depressive symptoms and the metabolic syndrome. For instance, Hildrum et al.[13] found no association between depressive symptoms and the metabolic syndrome after adjustment for physical activity and education in a sample of 9571 participants aged 20-89 years. This absence of association was consistent across sex and age groups. Important to note is that this study did find an association between depressive symptoms and waist circumference. In fact, the cross-sectional results from this thesis and of nearly all other cross-sectional studies revealed that waist circumference is (one of) the most important metabolic syndrome component in association with depressive symptoms. This stresses the importance of not just examining the metabolic syndrome as a whole, but to always include analyses on the different metabolic abnormalities.

Table 1. Associations between depression and metabolic syndrome (components) across thesis chapters

C	Study	Population [a]	Design	MS	AO	TRI	HDL	BP	GLU
2	Health ABC	2917 US black & white	X	+ [b]	+	+/	/	+	/
3	InCHIANTI	867 Italians	X						
		Overall		+	+/	/	+/	/	/
		Hyper-cortisolemic		+	+	+	+	/	/
4	LASA	1212 Dutch	X						
		Subthreshold		-	-	/	-	/	/
		MDD		/	/	/	/	/	/
5	Health ABC	2088 US black & white	L1	NA	+	NA	NA	NA	NA
6	Health ABC	2540 US black & white	L2	NA	+ [c]	NA	NA	NA	NA
7	InCHIANTI	823 Italians	L2						
		Onset		/	+	/	/	/	/
		Persistence		+	+/	+/	+/	+/	/

C = Chapter number; MS = metabolic syndrome; AO = abdominal obesity; TRI = high triglyceride levels; HDL = low high-density lipoprotein cholesterol levels; BP = high blood pressure; GLU = high fasting glucose levels; MDD = major depressive disorder; X = cross-sectional; L1 = longitudinal: depression -> metabolic syndrome; L2 = longitudinal: metabolic syndrome -> depression; + = positive association; / = no association; - = negative association; +/ = non-significant positive association; NA = not assessed. [a] All studies were conducted in the general older population; [b] only in white persons; [c] only in men.

Altogether, the somewhat inconsistent findings on the cross-sectional association between depression and the metabolic syndrome in the present thesis are also seen in other research reports. A plausible explanation for these discrepancies might be that the metabolic syndrome is only associated with a specific subtype of depression. In Chapter 3 it was found that only those older depressed persons who showed signs of a hyperactive HPA-axis - i.e. increased urinary cortisol levels - more often had the metabolic syndrome. Conversely, in Chapter 4, in which depressed persons were more likely to present with hypocortisolemia, the odds of metabolic syndrome were not increased. These findings illustrate the importance of considering and searching for depression subtypes when relating depression to somatic health conditions. Identifying depression subtypes could also greatly improve treatment of both depression and somatic health consequences as it becomes more clear to whom specialized treatment efforts should be addressed.

Does depression predict metabolic syndrome onset?

Evidence, so far, is thus only partly supportive of a cross-sectional association between depression and the metabolic syndrome. This does, however, not necessarily exclude the possibility of a longitudinal relationship. Is there evidence that depression could predict the onset of the metabolic syndrome? The findings of this thesis can only partly answer this question. In Chapter 5 it was shown that among older persons depressive symptoms were followed by an increase in abdominal obesity, in particular excess visceral fat (see Table 1). This confirmed earlier observations in a small sample size study by Weber-Hamann et al.,[14] which showed a larger accumulation of visceral fat mass over time in 29 depressed patients compared to 17 controls. Abdominal obesity, especially visceral fat, is often regarded as a principal causative factor in the metabolic syndrome.[15-17] At least, it is agreed upon that persons with abdominal obesity are more likely to become insulin resistant and to develop other metabolic disturbances.[18,19] Therefore, the results of this thesis certainly underline the possibility that depression might bring about metabolic abnormalities as seen in the metabolic syndrome. Only recently, a very few studies have investigated whether depressive symptoms predict onset of the full metabolic syndrome. Räikkönen et al.[20,21] showed that depressive symptoms increased the risk of metabolic syndrome onset after both 7 and 15 years of follow-up in a sample of 425 middle-aged women. Also, Goldbacher et al.[22] and Vanhala et al.[23] observed approximately two-fold increased risks of metabolic syndrome onset after 7 years of follow-up in middle-aged depressed women. Only Vanhala et al. also examined men, but did not find a risk difference of metabolic syndrome onset in men. Individual metabolic syndrome components were investigated by both Goldbacher et al. and Vanhala et al., and they found strongest associations for waist circumference and high-density lipoprotein cholesterol, respectively. Thus, although available studies are limited, both this thesis and other research, support the view that depression might increase the risk of onset of the metabolic syndrome, most convincingly abdominal obesity and associated lipid abnormalities.

Does depression follow metabolic syndrome?

There are thus strong indications that depression might predict the onset of the metabolic syndrome. As suggested in Chapter 1, it is, however, also very plausible that depression is a consequence of the metabolic syndrome. What is the support of this notion from this thesis and other research? Findings of this thesis related to this question are also summarized in Table 1. The results of Chapter 6 show that in an older population, obesity and in particular abdominal obesity, increases the risk of new depression onset, albeit only in men. Chapter 7 examined all metabolic syndrome components and concluded that abdominal obesity, but no other metabolic abnormalities, are indicative of an increased odds of the onset of depressive symptoms, consistent across sex. A few other recent studies have examined the relationship between the metabolic syndrome and depressive symptoms onset. Two large studies in middle-aged populations[24,25] and one large study among older persons[26] found that the metabolic syndrome increases the risk of depressive symptoms onset in both men and women. Risk estimates ranged from increased odds of depressive symptoms onset of 1.4 to 2.2. Two of these studies[24,25] found strongest associations for abdominal obesity and

lipid disturbances. Taken together, these findings suggest that depression might be a consequence of metabolic abnormalities, with strongest evidence for abdominal obesity and obesity-related factors (i.e. lipid disturbances).

If metabolic disturbances can induce depressive symptoms, then it might be questioned whether they can also promote depressive symptoms after they have emerged. That is, does the metabolic syndrome stimulate the persistence of depressive symptoms? The results of Chapter 6 show that (abdominal) obesity in older men is even more strongly associated with the onset of persistent depressive symptoms (2-fold increased risk when having excessive visceral fat) than with the onset of a single depression episode (1.3-fold increased risk). Moreover, in Chapter 7 it was found that the metabolic syndrome, with contributions of all metabolic syndrome components except glucose, predicted the persistence of depressive symptoms. Beyond this thesis, research on the relationship between the metabolic syndrome and the persistence of depressive symptoms is principally lacking. One recent study showed that adult men with the metabolic syndrome were more likely to have had experienced long-term depressive symptoms, although it was not clear whether metabolic syndrome was more strongly associated with long-term than with short-term depressive symptoms.[10] In all, the evidence to date suggests that the metabolic syndrome is associated with persistent depressive symptoms or, to put it differently, presence of the metabolic syndrome identifies a chronic depressive subtype.

Vicious cycle

From the above, it can be concluded that the evidence of a cross-sectional association between depression and the metabolic syndrome is somewhat inconsistent. However, the support for a longitudinal association between depressive symptoms and the metabolic syndrome appears more consistent, although, to date, less examined. Previous reports have observed stronger effects for longitudinal than cross-sectional associations. For instance, Kendler et al.[27] found only a modest lifetime association between major depression and coronary artery disease, but in time-dependent-models, associations between depression and coronary artery disease were much stronger. It might be reasoned, if there is a time-lag between the emergence of two conditions, that when examining the presence of both conditions at one moment in time, it is less likely that both conditions will be present compared to examining the presence of these conditions across time. Furthermore, a temporal association is generally considered to be stronger evidence of a causal relationship than a cross-sectional association. Therefore, finding stronger longitudinal than cross-sectional associations does actually support a causative rather than an associative relationship, although definite conclusions on causal relationships are very hard to draw from observational studies.

As was described above, support is found for both depressive symptoms predicting the onset of the metabolic syndrome, and the metabolic syndrome predicting the onset of depressive symptoms. Most compelling evidence exists for a bidirectional relationship between depressive symptoms with abdominal obesity and obesity-related factors (unhealthy lipid profile), but in particular visceral fat. This suggests a vicious cycle between depression and visceral fat accumulation. A schematic representation of this vicious cycle is

presented in Figure 1. The reciprocal relationship between depression and visceral fat accumulation possibly exists through related hyperactivity of the HPA-axis. Furthermore, once a person enters this vicious cycle, other metabolic syndrome abnormalities, provoked by high visceral fat, contribute to the persistence of depressive symptoms. In addition, the metabolic syndrome increases the risk of cardiovascular disease, which explains why depression and cardiovascular disease are associated. Cardiovascular disease, in turn, might exacerbate depressive symptoms via alternative pathways, e.g. decreased energy level, increased physical disability, or having to cope with disease. This notion of a vicious cycle between depression and metabolic disturbances makes clear that these two conditions are very much intertwined with large overlap in underlying pathophysiology. Therefore, it might be suggested that when occurring together, both depressive symptoms and metabolic disturbances are in truth two aspects of the same condition, which could be labeled as metabolic depression.

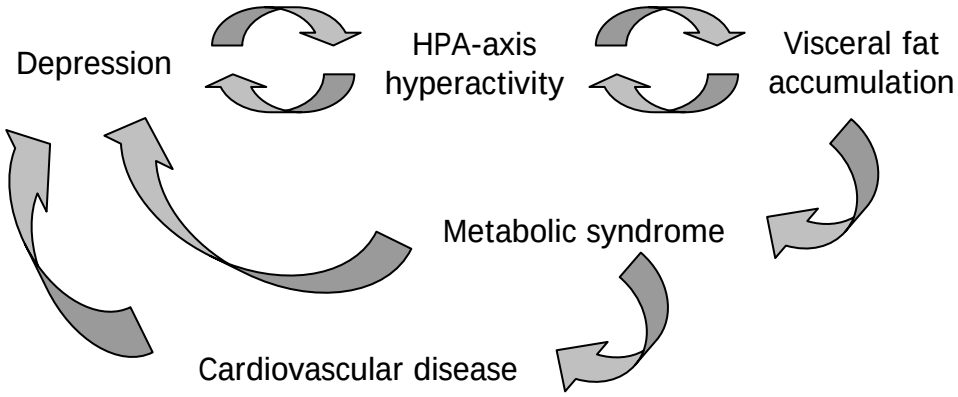

Figure 1. Vicious cycle between depression, visceral fat accumulation, metabolic syndrome and cardiovascular disease.

HPA = hypothalamic-pituitary-adrenal

Role of the HPA-axis

One aim of this thesis was to assess whether the HPA-axis plays a role in the relationship between depression and the metabolic syndrome. Activity of the HPA-axis is essential during stressful situations, but chronic stress might result in a hyperactive HPA-axis.[28] Furthermore, hyperactivity of the HPA-axis has recurrently been noted in at least a subset of depressed persons[29-32] and, in turn, high levels of cortisol have been associated with individual metabolic abnormalities, such as high blood pressure, insulin resistance, and obesity.[33,34] Specifically, research has suggested that cortisol promotes the accumulation of visceral fat by activating lipoprotein lipase and inhibiting lipid mobilization.[35] Visceral fat is highly sensitive to cortisol owing to a high density of glucocorticoid receptors.[36] Consequently, it

has been hypothesized that chronic stress and/or depression results in abdominal obesity and associated comorbidities through long-term activation of the HPA-axis.[35,37] This thesis examined the role of the HPA-axis in Chapters 3 and 4. In Chapter 3 a profound role of cortisol was uncovered. The cross-sectional association between depressive symptoms and the metabolic syndrome largely disappeared after appropriate adjustment for urinary cortisol levels. This indicates a mediating role of high cortisol levels in the association between depression and the metabolic syndrome. Moreover, it was found that only those depressed persons that presented with hypercortisolemia were at increased odds of having the metabolic syndrome. In Chapter 4, although no association was found between depression and the metabolic syndrome, serum cortisol levels were associated with the metabolic syndrome. This again suggests that when depressed persons present with hypercortisolemia, the odds of metabolic syndrome are increased. The findings in this thesis are corroborated by two other recent studies in which cortisol levels appeared to play a mediating role between depression and the metabolic syndrome.[38,39]

It was unexpected to find no association or even evidence of a reversed association between depression and the metabolic syndrome in Chapter 4. However, an explanation for this discrepancy might actually be found when considering cortisol levels. Previous reports among older persons have suggested that depressed persons are not only more likely to have hypercortisolemia, but might in fact also more often exhibit hypocortisolemia.[40,41] Hypocortisolemia could possibly be the result of exhaustion of the body's responses to stress.[42] In fact, in the Longitudinal Aging Study Amsterdam (LASA), on which the results of Chapter 4 are based, hypocortisolemia was more present among depressed persons than hypercortisolemia.[40] Thus, low levels of cortisol among a large part of the depressed group could actually have counterbalanced, or even reversed, the association between depression and the metabolic syndrome. Other studies have reported protective effects of low cortisol on metabolic factors.[42,43] Unfortunately, the number of major depression cases in LASA was too small to directly compare hypo- versus hypercortisolemic depressed persons in their likelihood of the metabolic syndrome.

Whether hypoactivity of the HPA-axis in depression is specific to an aging population is not entirely clear. Usually, aging is associated with an increase in basal cortisol levels and an increased cortisol response to challenge.[44-46] It has been suggested that hyperactivity of the HPA-axis in aging might be the result of the 'wear and tear' of a lifelong exposure to stress.[45] However, different stress-related disorders, such as post traumatic stress disorder, fibromyalgia, chronic fatigue syndrome, and burn-out, have been linked to hypocortisolemia, possibly after prolonged periods of hyperactivity of the HPA-axis.[42] Lifelong exposure to stress might therefore in some older persons actually lead to exhaustion of stress responses and associated hypocortisolemia.

One striking result from Chapters 3 and 4 needs some additional attention. In Chapter 3 it was concluded that hypercortisolemic depression was especially associated with the obesity-related components of the metabolic syndrome. Considering the role of cortisol in visceral fat accumulation and the important status of abdominal obesity within the metabolic syndrome, this result was definitely expected. However, in Chapter 4, although serum cortisol levels were associated with the metabolic syndrome and most of its components, no

association with waist circumference was found. If anything, serum cortisol levels showed a negative association with waist circumference. This inconsistency may, however, be explained by the measure of cortisol used. Urinary cortisol levels over a 24-h period provide a rather stable indicator of the total cortisol excretion by the adrenals and measure the biologically active (unbound) cortisol non-invasively.[47] In contrast, morning cortisol levels in blood do not represent the biological active cortisol and could possibly be increased by an acute stress reaction due to the blood draw itself. In Chapter 4 this was partly accounted for by calculating a cortisol free index, however a single measure of cortisol at one time-point may be less reliable than a 24-h index. What is even more important, research has suggested that in obese persons, cortisol secretion might be increased, but this might be coupled with an increased metabolic clearance of cortisol.[48,49] Therefore, when measured in serum or plasma, cortisol levels may be found to be decreased, while in urine they are increased, reflecting HPA-axis hyperactivity.

To summarize, this thesis illustrates that cortisol likely plays an important role in the link between depression and the metabolic syndrome, such that only hypercortisolemic depressed persons show an increased prevalence of the metabolic syndrome. As the designs of the studies used were cross-sectional it is difficult to draw conclusions on the direction of mediation by cortisol in the depression-metabolic syndrome relationship. Considering that depression could be caused by, or in itself could be regarded as, a chronic stressor and that the accumulation of visceral fat could be due to actions of cortisol, this seems to suggest a pathway from depression to metabolic syndrome. However, HPA-axis hyperactivity has been noted before the onset of depression[50] and is also present in obese persons who are not depressed,[51] implying a possible reverse direction. The role of cortisol within the vicious cycle of depression, visceral fat accumulation, and metabolic syndrome is depicted in Figure 1.

Other potential underlying pathways

The HPA-axis plays an important role in the association between depression and the metabolic syndrome, but other possible pathways are likely to contribute as well. These will shortly be addressed below.

Psychological and behavioral pathways

Psychological factors that may underlie an association between depression and the metabolic syndrome include a poor self-image or perceived stigma in those persons who are obese.[52] Also, persons with the metabolic syndrome might feel depressed about having to cope with their condition. Furthermore, depressed persons might have poorer health habits, e.g. they exercise less or have more fat intake, thereby increasing their metabolic risk. These explanations probably do not significantly contribute to the link between depression and the metabolic syndrome. In this thesis it was clearly found that associations with depression were specific to abdominal obesity, more strongly and independent of overall obesity. Comparable associations with overall obesity would be expected if psychological or behavioral mechanisms were at hand. Furthermore, in all analyses adjustments for lifestyle variables (smoking behavior, alcohol intake, physical activity) were made, which hardly

changed any of the findings. No information was available on diet, so it is possible that depressed persons had a poorer dietary pattern. However, again, a poor diet in itself would likely lead to an increase in both overall and abdominal obesity.[53] In combination with a hyperactive HPA-axis, however, it is possible that excess caloric intake is preponderantly stored into visceral fat depots.[54]

Somatic pathways

Cardiovascular disease and diabetes

Abundant evidence supports an association between depression with cardiovascular disease[55-61] and diabetes.[62-65] In this thesis it is postulated that depression might increase the risks of these two major outcomes by promoting the occurrence of the metabolic syndrome. Although the metabolic syndrome is often thought of as a precursor of diabetes or cardiovascular disease, the definition of metabolic syndrome does in itself not explicitly exclude the presence of these two diseases.[66] Therefore, it is possible, when a relationship between depression and the metabolic syndrome is found, that this is in fact due to an increased presence of diabetes or cardiovascular disease among persons with the metabolic syndrome. However, in this thesis we either adjusted for cardiovascular disease or diabetes, performed additional analyses excluding persons with prevalent diseases, and/or tested for interaction effects for the presence or absence of cardiovascular disease or diabetes. These analyses consistently confirmed that associations between depression and metabolic syndrome exist independent of cardiovascular disease or diabetes.

General health status

Next to cardiovascular disease and diabetes, a poor general health status should be considered a confounder when linking depression with obesity or the metabolic syndrome. Poor general health is usually linked with both depression and the presence of multiple somatic conditions.[67] Especially in old age, the importance of somatic health aspects increases. Because in older persons physical complaints and somatic conditions are very prevalent, the presence of these conditions should be considered since they can affect results when relating mental to physical health. Depression that first emerges in late-life is more often accompanied by somatic problems, possibly representing a different concept than early-life onset depression. In addition, somatic conditions might alter lifestyle behaviors (e.g. quit smoking or decrease physical activity), which then indirectly confound an association between depression and the metabolic syndrome. In this thesis adjustments for both general health status and lifestyle behaviors were consistently made, which little affected results.

Biological pathways

Inflammation

Inflammation is characterized by a chronic mildly elevated activity of the immune system which is illustrated by higher levels of, for example, C-reactive protein (CRP) and interleukin (IL)-6. With aging, inflammation levels generally increase steadily over time, thereby reaching levels that are closer to critical levels at which health impacts could occur. IL-6 has

been termed the 'cytokine for gerontologists'.[68] Although it has been linked with poor health in younger samples as well, its role in aging populations is eminent and striking. High levels of IL-6 have been linked to a large range of unfavorable health outcomes in older populations, varying from overall mortality, onset of cardiovascular disease, lung disease, cancer, frailty and physical decline.[69-76] Consequently, inflammation is considered to be a very general biological risk factor that could be an interlinking mechanism between different disease processes.

Inflammation is also critically involved in the metabolic syndrome. Inflammatory markers have been linked to obesity, lower high-density lipoprotein cholesterol levels, and higher triglycerides and fasting glucose concentrations.[77,78] Moreover, several studies have notably confirmed an association between CRP, IL-6, tumor necrosis factor-alpha, and fibrinogen with the metabolic syndrome.[79,80] It has even been postulated that inflammatory markers should be included in metabolic syndrome definitions.[80,81] One explanation for this strong association between inflammation and the metabolic syndrome is the release of cytokines by (visceral) fat depots.[79,82] Next to its association with the metabolic syndrome, chronic low-grade inflammation has been suggested to play a role in depression as well.[83] Depressed persons are found to have higher levels of CRP, IL-1 and IL-6, which could be a two-way association. One direction might be via the HPA-axis. Although the HPA-axis in normal situations should temper inflammatory reactions, prolonged hyperactivity of the HPA-axis could result in blunted anti-inflammatory responses to glucocorticoids resulting in increased inflammation.[84] A recent study indeed found that depressive symptoms predicted 6-year increases in IL-6.[85] A reverse association is also plausible as administration of pro-inflammatory cytokines (for instance in cancer or hepatitis C treatment) has consistently been shown to induce depression in about a third of patients.[86] One recent study was able to show that an association between depressive symptoms and the metabolic syndrome was partly mediated by inflammation, although an independent association of depressive symptoms with the metabolic syndrome remained.[87]

Sex steroid hormones

One other biological pathway could be through sex steroid hormones, as low levels of testosterone and dehydroepiandrosterone sulfate (DHEA-S) have been associated with major depression.[88] Alternatively, low levels of sex steroid hormones have been linked to various metabolic abnormalities.[89,90] Specifically, sex steroid hormones exert opposite effects compared to cortisol. Sex steroid hormones inhibit lipoprotein lipase synthesis and stimulates lipid mobilization, thereby reducing visceral fat depots.[35] When levels of sex steroid hormones are low, the visceral fat reducing effect is diminished, resulting in a larger accumulation of visceral fat, especially in the presence of high cortisol levels. The role of sex steroid hormones might be in particular important in older persons as with aging, and especially after menopause, levels of sex steroid hormones, such as testosterone, estradiol and DHEA-S, decrease.[91,92] It needs to be shown whether sex steroid hormones indeed play a mediating role in the relationship between depression and the metabolic syndrome.

Vascular depression

The vascular depression hypothesis[93] states that vascular damage in the brain might predispose, precipitate, or perpetuate depression in the elderly. More specifically, this hypothesis suggests that small vessel damage in frontal and subcortical regions of the brain, which play key roles in mood regulation, might increase the risk of depression. Indeed, magnetic resonance imaging of older depressed patients has revealed structural abnormalities in frontal-subcortical brain regions.[94] This vascular damage may be caused by continuing and profound influence of vascular risk factors, possibly including or resulting from metabolic abnormalities, inflammation or hypercortisolemia.

Hypercortisolemic, metabolic and vascular depression

Throughout this thesis different names for depressive subtypes were introduced, including hypercortisolemic depression, metabolic depression and vascular depression. What is the relationship between these concepts and how do they identify different subtypes? To start with, these three conditions definitely overlap. As was shown in this thesis, hyperactivity of the HPA-axis is plausibly involved in the association between depression and the metabolic syndrome. In fact, depressed persons with hypercortisolemia were at increased risk of having metabolic syndrome (Chapter 3). However, there is still a significant proportion of hypercortisolemic depressed persons that does not have the metabolic syndrome and depressed persons with the metabolic syndrome do not always show hypercortisolemia. Similarly, some persons with metabolic depression might have vascular brain lesions resulting in vascular depression, but as shown in Chapter 7, it is very likely that a metabolic depression exists apart from profound vascular damage. In turn, vascular depression does not have to be the result of metabolic disturbances. Thus, although the concepts of hypercortisolemic, metabolic, and vascular depression overlap, they certainly are not the same. Hypercortisolemic depression might increase the risk of metabolic depression, which increases the risk of vascular depression, but this is not a definite road to go and other factors promote the occurrence of metabolic and vascular depression. The benefit of identifying these different subtypes is that, besides from stimulating research into the pathophysiology of depression, it gives hints for both prevention and treatment of depression and its consequences. Treating hypercortisolemia in depressed persons might in theory both resolve depression and prevent metabolic disturbances. Managing metabolic disturbances in depressed persons might possibly improve depression prognosis and prevent further vascular damage throughout the body as well as the brain.

Metabolic syndrome: is it truly a syndrome?

Up until here, this thesis has treated the metabolic syndrome as if it is truly an existing syndrome, which can be related to other health aspects. However, in scientific literature some debate still exists whether it really is a unique condition. Arguments against the existence of the metabolic syndrome include the seemingly absence of one underlying causative factor, a lack of consensus on components to be included, and the limited evidence of increased predictive value of the metabolic syndrome beyond the risks from individual components.[19] These arguments indeed question the current metabolic syndrome

definition, but do not maintain that the concept of a metabolic condition should be disregarded. Most scientists do belief that several metabolic factors tend to cluster and occur together more often than by change alone. The doubts that are being raised should in fact stimulate more research into this metabolic concept, to eventually come to a definition that describes an etiological coherent condition and/or identifies persons at specific high-risk of developing diabetes or cardiovascular disease. Up until now the use of a metabolic syndrome definition in research has resulted in an impressive expansion of insight into pathophysiological processes underlying the occurrence of diabetes and cardiovascular disease as well as of associated diseases, such as depression. The main benefit of the metabolic syndrome concept for research purposes is that cardiovascular risk factors are not investigated in isolation, but multiple factors are being considered at once and their relative effects can be compared.

Cardiovascular disease

This thesis focuses on the relationship between depression and the metabolic syndrome. However, as was shown in Chapter 1, Figure 1, cardiovascular disease forms an important component of the research model investigated in this thesis. Several relationships with cardiovascular disease form the basis of this thesis and are assumed in this model. These are: associations of cardiovascular disease with 1) depression; 2) HPA-axis hyperactivity; and 3) the metabolic syndrome. A relationship between the metabolic syndrome and cardiovascular disease is not only very likely to exist - as all components of the metabolic syndrome represent individual cardiovascular risk factors - but has also been proven to exist by a multitude of studies.[95-101] The other two presumed relationships deserve somewhat more attention. First, although many studies have shown that depression predicts cardiovascular events and mortality in the general population, is a prognostic indicator of poor cardiovascular outcome in heart patients, and shows an increased onset after cardiovascular events, convincing evidence from the psychiatric patients' perspective was still lacking. In this thesis, in Chapter 9, it was confirmed in a psychopathology-based sample that depression is associated with an increased likelihood of cardiovascular disease, although in fact this might be largely owing to comorbid anxiety. Although from this cross-sectional study the temporal direction between depression and cardiovascular disease remains unclear, strong associations were found among those with a psychiatric disorder onset before the age of 30, most likely before cardiovascular disease had occurred. These results give additional support to a hypothesized pathway from depression to metabolic syndrome to cardiovascular disease.

This leaves one other presumed association in the hypothesized model: does a hyperactive HPA-axis eventually result in cardiovascular end-points? Many studies have assumed that high cortisol levels give rise to cardiovascular disease, and have therefore suggested that cortisol might mediate an association between depression and cardiovascular disease.[37,102] Several studies have shown that cortisol is associated with multiple cardiovascular risk factors, such as high blood pressure, obesity, high glucose and cholesterol levels, the metabolic syndrome and atherosclerosis.[33,34,38,39,103,104] However, direct evidence for a relationship between cortisol and the onset of cardiovascular end-

points was very sparse. One study reported a cortisol/testosterone ratio to be predictive of incident ischemic heart disease in middle-aged men.[105] In a general older population, a morning plasma cortisol level was not associated with self-reported non-fatal cardiovascular disease.[106] The results of this thesis (Chapter 8) confirm the long speculated relationship between urinary cortisol levels and cardiovascular mortality in an older general population. Even more, it was shown that high urinary cortisol levels were exclusively related to cardiovascular mortality and not to other causes of mortality, demonstrating a specific damaging effect of a hyperactive HPA-axis to the cardiovascular system.

Anxiety and other psychosocial factors

This thesis has its primary focus on depression and depressive symptoms. However, some attention is given to anxiety and other psychosocial risk factors. Their role will be shortly discussed here. In Chapter 2, next to depressive symptoms, the cross-sectional association between anxiety symptoms, recent life events and inadequate emotional support with the metabolic syndrome was assessed. These factors all appeared to be associated with the metabolic syndrome, although anxiety symptoms only in men. What's more, a cumulative index of psychosocial risk factors was most strongly associated with the metabolic syndrome. When examining the relative importance of the different psychosocial risk factors, most consistent results were found for recent life events and inadequate emotional support. Possibly, direct stressors through activation of the HPA-axis exert stronger effects on metabolic processes. Nevertheless, depressive symptoms are unrecognizably associated with the metabolic syndrome as is portrayed in this thesis.

Examination of anxiety disorders in relation to cardiovascular disease in an adult population was included in Chapter 9. It not only appeared that anxiety disorders were strongly associated with the presence of coronary heart disease, but also it was shown that this association was stronger than for depression. In fact, the association between depression and cardiovascular disease was mainly owing to depressions' comorbidity with anxiety disorders. Although not frequently examined, a stronger association with cardiovascular disease for anxiety than for depressive disorders is reported by others.[107] In contrast, some studies describe an association between depression, but not anxiety, with the metabolic syndrome.[6,7] Pathophysiological pathways linking depression versus anxiety with cardiovascular disease might partly differ. Together these results at least suggest that anxiety disorders are important to consider when relating depression and other mental health aspects to cardiovascular risk factors or disease.

Depressive symptoms versus diagnosis

Most of the chapters included in this thesis made use of the Center for Epidemiologic Studies-Depression (CES-D) scale[108] to assess depressive symptoms. Although this scale can detect the presence of clinically relevant depressive symptoms[109] it does not equal a depressive disorder diagnosis. The most important differences is that to fulfill criteria for a major depressive disorder diagnosis, key symptoms (depressed mood and/or lack of interest) must be experienced. In contrast, the CES-D, as most other depressive symptoms checklists, regards all symptoms as equal and makes a count of the number of depressive

symptoms present, without requirement of the presence of key symptoms. Depressive symptom checklists in general contain a considerable number of somatic symptoms, e.g. fatigue, sleep problems and appetite or weight changes. Persons with many somatic health problems, which are especially common in older persons, could theoretically score high on this depressive symptoms questionnaire simply because of their somatic symptoms. This is important to realize when relating depressive symptoms to somatic health aspects. By adjusting analyses for physical factors, both lifestyle factors and disease and health-related factors, the possible influence of depression misclassification due to somatic symptoms was tried to kept to a minimum in this thesis. Besides, despite the theoretic possibility of misclassification, the CES-D has been proven to be a valid and reliable instrument and has shown very good sensitivity and specificity when identifying major depressive disorder in older persons.[109]

Methodological considerations

Several methodological considerations have already been made throughout the current chapter. These include the possibility of information bias (e.g. assessing depression by means of symptoms checklists, defining the metabolic syndrome, measuring cortisol), properly taking into account possible confounding factors (e.g. lifestyle behaviors, general health aspects) and the restricted ability of drawing definite causal inferences from observational research. In this section additional comments on possible selection bias (selective survival) and generalizability will be made.

Nearly all the results in this thesis are based on older populations. By definition, when recruiting a sample of older persons, those who have already died are not included in the cohort. Also, during follow-up the less healthy are more likely to withdraw, to get lost or to die. It is essential to take into account the possibility of selective survival for a comprehensive interpretation of causality between mental and somatic health. It is certainly possible that examined risk factors are not predictive of diminished health, solely because those who were both exposed and affected by the risk factor of interest are no longer alive. For example, depression and life-events have found to be less predictive of mortality in the oldest (85 years and up) compared to the young old (70 to 84 years),[110,111] which could be partly explained by selective survival. These findings illustrate that selective survival tends to decrease the strength of investigated associations, but suggest that when associations are found (as in this thesis) in reality the relationship might be even stronger.

Furthermore, as mentioned before, in an older population somatic health problems are much more prevalent and depression that first emerges in late-life might be much more entangled with somatic conditions than depression that emerges earlier in life. On the other hand, competing (i.e. stronger) risk factors for health outcomes in old age, such as other somatic conditions, could override the effects of mental health factors. These considerations implicate that results of the present thesis cannot automatically be generalized to younger populations. However, as described in the first sections of this chapter, others have confirmed associations between depression and the metabolic syndrome in middle-aged and even younger study samples.

Public health & clinical implications

The prevalence of obesity is increasing alarmingly world-wide[112] and with it the prevalence of metabolic syndrome. Also, depression holds a top position among the list of diseases with high disease burden across the world, which will continue to rise over the next years.[113] Depression, obesity and metabolic syndrome are clearly not only of major public health interest, but also have profound impact on well-being and daily functioning of the individual, especially when occurring together and in older persons.[114-116] This thesis shows that a vicious cycle might exist between depressive symptoms and abdominal obesity, and in a later stage metabolic syndrome. Evidently, trying to prevent that persons enter this vicious cycle could greatly benefit public health as well as clinical care. It is important to realize that even if the intimate association between depression and metabolic syndrome is only present in older persons, pathophysiological processes leading to the rise of, for instance, metabolic depression are probably already occurring at younger ages. One possible way to prevent the occurrence of both metabolic syndrome and depression or to promote the reduction of depressive symptoms and metabolic abnormalities, might be to stimulate physical activity. Although physical activity does not appear to be an important confounder in the relationship between depression and the metabolic syndrome, this does not imply a lack of impact of physical activity on both conditions. In fact, multiple (randomized) controlled trials have shown that physical activity can decrease visceral fat depots and other metabolic abnormalities.[117,118] Furthermore, meta-analyzed evidence suggests that exercise can improve depressive symptoms to some degree.[119] Promoting physical activity can both be done within a public health and a clinical setting. Next to physical activity, promoting a general healthy life style (e.g. healthy diet) might be beneficial.

The above mentioned implications apply to public health as well as clinical care. From a clinical care perspective additional implications of the results of this thesis can be made. The results suggest that a clinician, regardless a psychiatrist, a general practitioner or a geriatrist, should be aware that depression and metabolic disturbances tend to co-occur, conceivably promote each other and possibly hinder treatment. The results of the present thesis show that 30-35% of depressed older persons have the metabolic syndrome; even higher prevalences are found in the hypercortisolemic depressed (42%). This implicates that a significant proportion of depressed persons might benefit from assessment of the presence of metabolic abnormalities as treating these secondary conditions could improve general health status of these patients and possibly prevent subsequent disease (i.e. diabetes and cardiovascular disease). Whether treatment of metabolic disturbances could improve depression prognosis and whether treatment of depressive symptoms could improve the metabolic profile needs to be examined.

Future research

The present thesis provides evidence for the concept of a metabolic depression, which represents a chronic depressive subtype associated with metabolic disturbances. Future research should confirm the existence of such a condition in men and women in both older and younger populations using prospective designs. In addition, the temporal associations between depression, HPA-axis hyperactivity, and the metabolic syndrome need to be further

explored to help improve prevention and treatment of depression as well as metabolic syndrome. Next to these more or less 'confirmatory' investigations, more innovative research is needed as well. Other pathophysiological mechanisms apart from the HPA-axis may underlie or might be involved in the relationship between depression and metabolic syndrome, such as chronic low-grade inflammation. Research has only just begun to unravel the role of inflammation as mediating factor between depression and metabolic or cardiovascular risks. What's even more unexplored is the role of possible genetic influences that might explain some of the found associations between depression, visceral fat accumulation and the metabolic syndrome. Possibly, genetic factors are (partly) responsible for the vicious cycle as presented in this thesis. When known, treatment could be targeted at the biological systems that are regulated by these genetic factors. Another aspect that needs to be more elaborately explored is the role of anxiety disorders. In general, research on the link between mental and somatic health aspects has focused on depression, leaving anxiety relatively untouched. The results of Chapter 9, however, suggest that anxiety disorders are very important to consider as well. Lastly, there is a pressing need for intervention studies examining whether treatment of either depression or metabolic abnormalities could relieve or prevent symptoms of the other condition. Ultimately, an integrated intervention program for persons with metabolic depression, addressing both depression and metabolic syndrome should be tested for its capability of treating both conditions at once.

In conclusion

Depression and abdominal obesity appear to have a two-directional relationship. When both conditions are present, additional metabolic abnormalities might promote a chronic character of the depressive symptoms. These results are suggestive of a vicious cycle and are indicative of the existence of a specific condition, which might be labeled as metabolic depression. Although the notion of a vicious cycle and a chronic depressive subtype suggests a poor prognosis, the implications of this thesis are positive as well. As depression and metabolic disturbances are in principal treatable conditions, this gives hope for a better prognosis of metabolic depression. Knowing that depression and metabolic syndrome often do not occur in isolation has direct implications for prevention and treatment of both conditions.

References

1. Dunbar JA, Reddy P, vis-Lameloise N et al. Depression: an important comorbidity with metabolic syndrome in a general population. *Diabetes Care.* 2008;31:2368-2373.
2. Gil K, Radzillowicz P, Zdrojewski T et al. Relationship between the prevalence of depressive symptoms and metabolic syndrome. Results of the SOPKARD Project. *Kardiol Pol.* 2006;64:464-469.
3. Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP. Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. *Psychosom Med.* 2004;66:316-322.
4. McCaffery JM, Niaura R, Todaro JF, Swan GE, Carmelli D. Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. *Psychosom Med.* 2003;65:490-497.

5. Miettola J, Niskanen LK, Viinamaki H, Kumpusalo E. Metabolic syndrome is associated with self-perceived depression. *Scand J Prim Health Care.* 2008;26:203-210.
6. Skilton MR, Moulin P, Terra JL, Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. *Biol Psychiatry.* 2007;62:1251-1257.
7. Takeuchi T, Nakao M, Nomura K, Yano E. Association of metabolic syndrome with depression and anxiety in Japanese men. *Diabetes Metab.* 2009;35:32-36.
8. Toker S, Shirom A, Melamed S. Depression and the metabolic syndrome: gender-dependent associations. *Depress Anxiety.* 2007.
9. Vaccarino V, McClure C, Johnson BD et al. Depression, the metabolic syndrome and cardiovascular risk. *Psychosom Med.* 2008;70:40-48.
10. Viinamaki H, Heiskanen T, Lehto SM et al. Association of depressive symptoms and metabolic syndrome in men. *Acta Psychiatr Scand.* 2009;120:23-29.
11. Carroll D, Phillips AC, Thomas GN, Gale CR, Deary I, Batty GD. Generalized anxiety disorder is associated with metabolic syndrome in the Vietnam experience study. *Biol Psychiatry.* 2009;66:91-93.
12. Herva A, Rasanen P, Miettunen J et al. Co-occurrence of metabolic syndrome with depression and anxiety in young adults: the Northern Finland 1966 Birth Cohort Study. *Psychosom Med.* 2006;68:213-216.
13. Hildrum B, Mykletun A, Midthjell K, Ismail K, Dahl AA. No association of depression and anxiety with the metabolic syndrome: the Norwegian HUNT study. *Acta Psychiatr Scand.* 2009;120:14-22.
14. Weber-Hamann B, Werner M, Hentschel F et al. Metabolic changes in elderly patients with major depression: evidence for increased accumulation of visceral fat at follow-up. *Psychoneuroendocrinology.* 2006;31:347-354.
15. Anderson PJ, Critchley JA, Chan JC et al. Factor analysis of the metabolic syndrome: obesity vs insulin resistance as the central abnormality. *Int J Obes Relat Metab Disord.* 2001;25:1782-1788.
16. Carr DB, Utzschneider KM, Hull RL et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. *Diabetes.* 2004;53:2087-2094.
17. Maison P, Byrne CD, Hales CN, Day NE, Wareham NJ. Do different dimensions of the metabolic syndrome change together over time? Evidence supporting obesity as the central feature. *Diabetes Care.* 2001;24:1758-1763.
18. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005;112:2735-2752.
19. Kahn R. Metabolic syndrome: is it a syndrome? Does it matter? *Circulation.* 2007;115:1806-1810.
20. Raikkonen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? *Metabolism.* 2002;51:1573-1577.
21. Raikkonen K, Matthews KA, Kuller LH. Depressive symptoms and stressful life events predict metabolic syndrome among middle-aged women: a comparison of World Health Organization, Adult Treatment Panel III, and International Diabetes Foundation definitions. *Diabetes Care.* 2007;30:872-877.
22. Goldbacher EM, Matthews KA. Are psychological characteristics related to risk of the metabolic syndrome? A review of the literature. *Ann Behav Med.* 2007;34:240-252.
23. Vanhala M, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Koponen H. Depressive symptoms predispose females to metabolic syndrome: a 7-year follow-up study. *Acta Psychiatr Scand.* 2009;119:137-142.
24. Akbaraly TN, Kivimaki M, Brunner EJ et al. Association between metabolic syndrome and depressive symptoms in middle-aged adults: results from the Whitehall II study. *Diabetes Care.* 2009;32:499-504.
25. Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S, Kumpusalo E, Vanhala M. Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry.* 2008;69:178-182.
26. Mast BT, Miles T, Penninx BW et al. Vascular disease and future risk of depressive symptomatology in older adults: findings from the Health, Aging, and Body Composition study. *Biol Psychiatry.* 2008;64:320-326.

27. Kendler KS, Gardner CO, Fiske A, Gatz M. Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. *Arch Gen Psychiatry.* 2009;66:857-863.
28. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA.* 1992;267:1244-1252.
29. Gillespie CF, Nemeroff CB. Hypercortisolemia and depression. *Psychosom Med.* 2005;67 Suppl 1:S26-S28.
30. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry.* 2002;7:254-275.
31. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci.* 2008;31:464-468.
32. Vreeburg SA, Hoogendijk WJ, van PJ et al. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Arch Gen Psychiatry.* 2009;66:617-626.
33. Brunner EJ, Hemingway H, Walker BR et al. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. *Circulation.* 2002;106:2659-2665.
34. Fraser R, Ingram MC, Anderson NH, Morrison C, Davies E, Connell JM. Cortisol effects on body mass, blood pressure, and cholesterol in the general population. *Hypertension.* 1999;33:1364-1368.
35. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? *Obes Rev.* 2001;2:73-86.
36. Bronnegard M, Arner P, Hellstrom L, Akner G, Gustafsson JA. Glucocorticoid receptor messenger ribonucleic acid in different regions of human adipose tissue. *Endocrinology.* 1990;127:1689-1696.
37. Rosmond R. Role of stress in the pathogenesis of the metabolic syndrome. *Psychoneuroendocrinology.* 2005;30:1-10.
38. Muhtz C, Zyriax BC, Klahn T, Windler E, Otte C. Depressive symptoms and metabolic risk: effects of cortisol and gender. *Psychoneuroendocrinology.* 2009;34:1004-1011.
39. Veen G, Giltay EJ, Derijk RH, van V, I, van PJ, Zitman FG. Salivary cortisol, serum lipids, and adiposity in patients with depressive and anxiety disorders. *Metabolism.* 2009;58:821-827.
40. Bremmer MA, Deeg DJ, Beekman AT, Penninx BW, Lips P, Hoogendijk WJ. Major depression in late life is associated with both hypo- and hypercortisolemia. *Biol Psychiatry.* 2007;62:479-486.
41. Penninx BW, Beekman AT, Bandinelli S et al. Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamo-pituitary-adrenal axis. *Am J Geriatr Psychiatry.* 2007;15:522-529.
42. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology.* 2005;30:1010-1016.
43. Hellhammer J, Schlotz W, Stone AA, Pirke KM, Hellhammer D. Allostatic load, perceived stress, and health: a prospective study in two age groups. *Ann N Y Acad Sci.* 2004;1032:8-13.
44. Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: importance of gender. *Psychoneuroendocrinology.* 2005;30:80-91.
45. Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *J Clin Endocrinol Metab.* 1996;81:2468-2473.
46. Veldhuis JD, Keenan DM, Roelfsema F, Iranmanesh A. Aging-related adaptations in the corticotropic axis: modulation by gender. *Endocrinol Metab Clin North Am.* 2005;34:993-9xi.
47. Yehuda R, Halligan SL, Yang RK et al. Relationship between 24-hour urinary-free cortisol excretion and salivary cortisol levels sampled from awakening to bedtime in healthy subjects. *Life Sci.* 2003;73:349-358.
48. Walker BR. Cortisol--cause and cure for metabolic syndrome? *Diabet Med.* 2006;23:1281-1288.
49. Ward AM, Syddall HE, Wood PJ, Dennison EM, Phillips DI. Central hypothalamic-pituitary-adrenal activity and the metabolic syndrome: Studies using the corticotrophin-releasing hormone test. *Metabolism.* 2004;53:720-726.
50. Wichers MC, Myin-Germeys I, Jacobs N et al. Susceptibility to depression expressed as alterations in cortisol day curve: a cross-twin, cross-trait study. *Psychosom Med.* 2008;70:314-318.
51. Pasquali R, Vicennati V, Cacciari M, Pagotto U. The hypothalamic-pituitary-adrenal axis activity in obesity and the metabolic syndrome. *Ann N Y Acad Sci.* 2006;1083:111-128.
52. Chen EY, Bocchieri-Ricciardi LE, Munoz D et al. Depressed mood in class III obesity predicted by weight-related stigma. *Obes Surg.* 2007;17:669-671.
53. Newby PK, Muller D, Hallfrisch J, Qiao N, Andres R, Tucker KL. Dietary patterns and changes in body mass index and waist circumference in adults. *Am J Clin Nutr.* 2003;77:1417-1425.

54. Dallman MF, la Fleur SE, Pecoraro NC, Gomez F, Houshyar H, Akana SF. Minireview: glucocorticoids--food intake, abdominal obesity, and wealthy nations in 2004. *Endocrinology.* 2004;145:2633-2638.
55. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med.* 2004;66:802-813.
56. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J.* 2006;27:2763-2774.
57. Frasure-Smith N, Lesperance F. Reflections on depression as a cardiac risk factor. *Psychosom Med.* 2005;67 Suppl 1:S19-S25.
58. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med.* 2002;23:51-61.
59. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry.* 2007;22:613-626.
60. van Melle JP, de JP, Spijkerman TA et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med.* 2004;66:814-822.
61. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med.* 2003;65:201-210.
62. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med.* 2006;23:1165-1173.
63. Cosgrove MP, Sargeant LA, Griffin SJ. Does depression increase the risk of developing type 2 diabetes? *Occup Med (Lond).* 2008;58:7-14.
64. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia.* 2006;49:837-845.
65. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care.* 2008;31:2383-2390.
66. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation.* 2002;106:3143-3421.
67. Stewart R, Hirani V. General health status and vascular disorders as correlates of late-life depressive symptoms in a national survey sample. *Int J Geriatr Psychiatry.* 2009.
68. Ferrucci L, Harris TB, Guralnik JM et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc.* 1999;47:639-646.
69. Barzilay JI, Blaum C, Moore T et al. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med.* 2007;167:635-641.
70. Cesari M, Penninx BW, Pahor M et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci.* 2004;59:242-248.
71. Ferrucci L, Penninx BW, Volpato S et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc.* 2002;50:1947-1954.
72. Gallucci M, Amici GP, Ongaro F et al. Associations of the plasma interleukin 6 (IL-6) levels with disability and mortality in the elderly in the Treviso Longeva (Trelong) study. *Arch Gerontol Geriatr.* 2007;44 Suppl 1:193-198.
73. Heikkila K, Ebrahim S, Lawlor DA. Systematic review of the association between circulating interleukin-6 (IL-6) and cancer. *Eur J Cancer.* 2008;44:937-945.
74. Kritchevsky SB, Cesari M, Pahor M. Inflammatory markers and cardiovascular health in older adults. *Cardiovasc Res.* 2005;66:265-275.
75. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *J Am Geriatr Soc.* 2007;55:864-871.
76. Yende S, Waterer GW, Tolley EA et al. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. *Thorax.* 2006;61:10-16.
77. Festa A, D'Agostino R, Jr., Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation.* 2000;102:42-47.

78. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA.* 1999;282:2131-2135.
79. Sutherland JP, McKinley B, Eckel RH. The metabolic syndrome and inflammation. *Metab Syndr Relat Disord.* 2004;2:82-104.
80. Devaraj S, Singh U, Jialal I. Human C-reactive protein and the metabolic syndrome. *Curr Opin Lipidol.* 2009;20:182-189.
81. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. *Am J Cardiol.* 2006;97:3A-11A.
82. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet.* 2005;365:1415-1428.
83. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med.* 2009;71:171-186.
84. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol.* 2002;21:531-541.
85. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. *Brain Behav Immun.* 2009;23:936-944.
86. Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon-alpha. *Biol Psychiatry.* 2004;56:819-824.
87. Capuron L, Su S, Miller AH et al. Depressive symptoms and metabolic syndrome: is inflammation the underlying link? *Biol Psychiatry.* 2008;64:896-900.
88. Morsink LF, Vogelzangs N, Nicklas BJ et al. Associations between sex steroid hormone levels and depressive symptoms in elderly men and women: results from the Health ABC study. *Psychoneuroendocrinology.* 2007;32:874-883.
89. Maggio M, Lauretani F, Ceda GP et al. Association between hormones and metabolic syndrome in older Italian men. *J Am Geriatr Soc.* 2006;54:1832-1838.
90. Maggio M, Lauretani F, Ceda GP et al. Association of hormonal dysregulation with metabolic syndrome in older women: data from the InCHIANTI study. *Am J Physiol Endocrinol Metab.* 2007;292:E353-E358.
91. Al-Azzawi F, Palacios S. Hormonal changes during menopause. *Maturitas.* 2009;63:135-137.
92. Sternbach H. Age-associated testosterone decline in men: clinical issues for psychiatry. *Am J Psychiatry.* 1998;155:1310-1318.
93. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry.* 1997;54:915-922.
94. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry.* 2000;57:1071-1076.
95. Butler J, Rodondi N, Zhu Y et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. *J Am Coll Cardiol.* 2006;47:1595-1602.
96. Dekker JM, Girman C, Rhodes T et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation.* 2005;112:666-673.
97. Holvoet P, Kritchevsky SB, Tracy RP et al. The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the health, aging, and body composition cohort. *Diabetes.* 2004;53:1068-1073.
98. Isomaa B, Almgren P, Tuomi T et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care.* 2001;24:683-689.
99. Lakka HM, Laaksonen DE, Lakka TA et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA.* 2002;288:2709-2716.
100. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. *BMJ.* 2006;332:878-882.
101. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in beaver dam. *Diabetes Care.* 2002;25:1790-1794.
102. Bjorntorp P. Heart and soul: stress and the metabolic syndrome. *Scand Cardiovasc J.* 2001;35:172-177.
103. Dekker MJ, Koper JW, van Aken MO et al. Salivary cortisol is related to atherosclerosis of carotid arteries. *J Clin Endocrinol Metab.* 2008;93:3741-3747.
104. Matthews K, Schwartz J, Cohen S, Seeman T. Diurnal cortisol decline is related to coronary calcification: CARDIA study. *Psychosom Med.* 2006;68:657-661.

105. Smith GD, Ben-Shlomo Y, Beswick A, Yarnell J, Lightman S, Elwood P. Cortisol, testosterone, and coronary heart disease: prospective evidence from the Caerphilly study. *Circulation.* 2005;112:332-340.
106. Schoorlemmer RM, Peeters GM, van Schoor NM, Lips P. Relationships between cortisol level, mortality and chronic diseases in older persons. *Clin Endocrinol (Oxf).* 2009;Accepted Article:doi: 10.1111/j.1365-2265-2009.03552.x.
107. Strik JJ, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J Am Coll Cardiol.* 2003;42:1801-1807.
108. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement.* 1977;1:385-401.
109. Beekman AT, Deeg DJ, van Limbeek J, Braam AW, De Vries MZ, van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med.* 1997;27:231-235.
110. Jordanova V, Stewart R, Goldberg D et al. Age variation in life events and their relationship with common mental disorders in a national survey population. *Soc Psychiatry Psychiatr Epidemiol.* 2007;42:611-616.
111. Rapp MA, Gerstorf D, Helmchen H, Smith J. Depression predicts mortality in the young old, but not in the oldest old: results from the Berlin Aging Study. *Am J Geriatr Psychiatry.* 2008;16:844-852.
112. World health Organization. Obesity. Preventing and managing the global epidemic. Report of a WHO consultation on obesity. 894. 2000. Geneva, WHO. Technical Report Series. Ref Type: Report
113. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3:e442.
114. Buist-Bouwman MA, de GR, Vollebergh WA, Alonso J, Bruffaerts R, Ormel J. Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. *Acta Psychiatr Scand.* 2006;113:492-500.
115. Penninx BW, Nicklas BJ, Newman AB et al. Metabolic syndrome and physical decline in older persons: results from the Health, Aging And Body Composition Study. *J Gerontol A Biol Sci Med Sci.* 2009;64:96-102.
116. Salihu HM, Bonnema SM, Alio AP. Obesity: What is an elderly population growing into? *Maturitas.* 2009;63:7-12.
117. Kay SJ, Fiatarone Singh MA. The influence of physical activity on abdominal fat: a systematic review of the literature. *Obes Rev.* 2006;7:183-200.
118. Lakka TA, Laaksonen DE. Physical activity in prevention and treatment of the metabolic syndrome. *Appl Physiol Nutr Metab.* 2007;32:76-88.
119. Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. *Cochrane Database Syst Rev.* 2009;CD004366.

Summary

Depression is a common mental disorder which causes high burden for both the community and the individual. According to the World Health Organization depression ranks high in the top ten of diseases with the highest disease burden due to a marked loss in quality of life. Also high in this top ten is cardiovascular disease. Depressed persons have approximately a two-fold increased risk of having or developing cardiovascular disease. Further, after a cardiovascular event the risk of onset of depression is increased, resulting in poorer cardiovascular outcome. Mechanisms underlying this comorbidity between depression and cardiovascular disease are still largely unknown. The metabolic syndrome, a constellation of cardiovascular risk factors including (abdominal) obesity, hypertension, dyslipidemia and hyperglycemia, has been suggested to be one possible pathway linking depression and cardiovascular disease. Evidence exists that metabolic disturbances might occur more frequently in depressed persons. Disturbed functioning of one of the most important stress systems of the human body, the hypothalamic-pituitary-adrenal (HPA)-axis, might underlie the association between depression and metabolic syndrome. Evidence for these hypotheses is largely confined to cross-sectional research and to investigation of individual as opposed to the combination of metabolic disturbances. Therefore, the general aim of this thesis is to examine whether depressive disorders or symptoms are associated with, predict or follow metabolic disturbances, such as present in metabolic syndrome. In addition, a possible mediating role of the HPA-axis in the relationship between depression on the one hand and metabolic syndrome and cardiovascular disease on the other hand is examined. Knowledge to be gained by this thesis could increase our understanding of pathophysiological processes linking depression and cardiovascular disease, which might be very useful for prevention and treatment of both conditions. To study these research questions data from several large prospective cohort studies are used. Focus is given to older populations as both depressive symptoms and cardiovascular conditions are highly prevalent among the aged. After the theoretical background and research model is presented in **Chapter 1**, Chapters 2 through 9 report on research outcomes.

First, the cross-sectional association between depression and metabolic syndrome is investigated. **Chapter 2** reports on data from the Health, Aging and Body Composition (ABC) study and examines the cross-sectional relationship between several psychosocial risk factors (depressive and anxiety symptoms, negative life events, and inadequate emotional support) and metabolic syndrome in a community-based sample of black and white older persons (N = 2917). All examined psychosocial risk factors were (modestly) associated with metabolic syndrome, although depressive symptoms only in white persons and anxiety symptoms only in men. A combined psychosocial risk index showed the strongest association with metabolic syndrome, which was not confined to a specific component of the metabolic syndrome. **Chapter 3** presents results from the InCHIANTI study among 867 persons aged 65 years and older. Also in this study, depressive symptoms and metabolic syndrome were associated. Findings from the Longitudinal Aging Study Amsterdam (LASA), including 1212 participants aged 65 years and older, are described in **Chapter 4.** However, results of this study did not show significantly increased odds of metabolic syndrome in

persons with major depressive disorder. Persons with subthreshold depressive symptoms even had a decreased odds of metabolic syndrome.

Next, a possible role of the HPA-axis in the association between depression and the metabolic syndrome is examined. Cortisol levels, from urine or blood, provide an index of HPA-axis activity. In **Chapter 3**, based on the InCHIANTI study, a profound role of cortisol is uncovered. The reported cross-sectional association between depressive symptoms and metabolic syndrome largely disappeared after appropriate adjustment for urinary cortisol levels. This indicates a mediating role of high cortisol levels in the association between depression and metabolic syndrome. Moreover, it was found that only those depressed persons that presented with hypercortisolemia were at increased odds of having metabolic syndrome. In particular, high levels of cortisol were associated with a large waist circumference, high triglyceride levels and low high-density lipoprotein cholesterol levels in depressed persons. Although no positive association was found between depression and metabolic syndrome in LASA (**Chapter 4**), results from this study did show that serum cortisol levels are associated with metabolic syndrome. This again suggests that when depressed persons present with hypercortisolemia, odds of metabolic syndrome are increased.

Subsequently, the temporal direction of associations between depression and metabolic syndrome is examined using longitudinal designs. Special focus is given to (abdominal) obesity as this is a central component in metabolic syndrome. **Chapter 5** examines whether depressive symptoms predict an increase in abdominal obesity using 5-year follow-up data from 2088 participants of the Health ABC study. This study showed that having depressive symptoms was followed by an increase in abdominal obesity, specifically visceral fat. This increase was independent of overall obesity, suggesting that there may be specific pathophysiological mechanisms that link depression with visceral fat accumulation. In **Chapter 6** the reverse direction is investigated in the Health ABC study, namely whether (abdominal) obesity increases the risk of onset of significant depressive symptoms in 2547 persons without depression at baseline. Both overall and abdominal obesity predicted onset of depressive symptoms over 5 years of follow-up in men, but not in women. When examined simultaneously, only the effect of visceral fat, but not overall obesity, was an independent predictor of depressive symptoms onset. Stronger associations were found for the onset of depressive symptoms that persisted. **Chapter 7** examines whether metabolic syndrome and its components are associated with both the onset and the chronicity of depressive symptoms using data from 823 participants of the InCHIANTI study. Higher waist circumference, but no other metabolic syndrome component, increased odds of depressive symptoms onset after 3 or 6 years in initially non-depressed persons. Among depressed persons, metabolic syndrome was associated with an almost 3-fold increased odds of persistence of depressive symptoms. Findings suggest that a vicious cycle between depression and visceral fat accumulation might eventually result in a chronic depressive subtype, characterized by metabolic disturbances (‘metabolic depression’).

Lastly, to make the research model complete, presumed associations between both HPA-axis hyperactivity and depression with cardiovascular disease are tested. HPA-axis activity has been linked to several cardiovascular risk factors, but it's effect on clinical cardiovascular endpoints has hardly been examined. **Chapter 8** again uses data from the InCHIANTI study to examine whether urinary cortisol levels predict all-cause and cardiovascular mortality over 6 years of follow-up among 900 participants. Persons having urinary cortisol levels in the top tertile had an almost 3-fold increased risk of dying of cardiovascular disease within 6 years. Risk of all-cause mortality was not increased. These findings confirm that high cortisol levels might be particularly damaging to the cardiovascular system. **Chapter 9** investigates whether the frequently reported association between depression and cardiovascular disease extents to a psychopathology-based sample, as evidence for this association almost exclusively comes from studies among heart patients or the general population. In addition, anxiety disorders are taken into account as they are often comorbid to depression. Data are from 2807 persons with current or remitted depressive or anxiety disorders and healthy controls of the Netherlands Study of Depression and Anxiety. Results show that persons with a current anxiety disorder were approximately three-fold more likely to have coronary heart disease. Increased prevalence of coronary heart disease among depressed persons was largely owing to comorbid anxiety.

The thesis ends with a general discussion (**Chapter 10**) of the findings of Chapters 2 through 9. Taken together, this thesis suggests that in older persons the association between depression and metabolic syndrome might be restricted to a specific subgroup of depressive patients, those that present with hyperactivity of the HPA-axis. In a longitudinal perspective, depressive symptoms and abdominal obesity appear to have a two-directional relationship. When both conditions are present, additional metabolic disturbances might promote a chronic character of the depressive symptoms. These results are suggestive of a vicious cycle and are indicative of the existence of a specific condition, which might be labeled as metabolic depression. Awareness of and appropriate monitoring of comorbid metabolic disturbances in depressed patients might improve their somatic health status and could possibly prevent subsequent cardiovascular disease. Whether treatment of metabolic disturbances could improve depression prognosis needs to be examined.

Samenvatting

Depressie is een veelvoorkomende psychische stoornis die een hoge ziektelast veroorzaakt voor zowel de samenleving als het individu. De Wereldgezondheidsorganisatie (WHO) heeft aangetoond dat depressie hoog in de top tien staat van ziektes met een hoge ziektelast. Dit komt vooral door de grote mate van verlies van kwaliteit van leven die gepaard gaat met depressie. Niet alleen depressie staat hoog in deze zogenaamde 'ziektelasten-lijst'. Ook hart- en vaatziekten veroorzaken in de wereld veel ziektelast door een combinatie van vroegtijdig overlijden en verlies van kwaliteit van leven. Mensen met een depressie hebben ongeveer tweemaal zoveel kans om een hartziekte te hebben of te ontwikkelen dan mensen die niet aan een depressie lijden. Bovendien heeft onderzoek uitgewezen dat depressie vaak ontstaat nadat iemand bijvoorbeeld een hartaanval heeft gehad. De depressie heeft weer een negatieve invloed op het herstel en verloop van een aanwezige hartziekte. Het is nog steeds voor een groot deel onbekend welke mechanismen ten grondslag liggen aan deze samenhang tussen depressie en hart- en vaatziekten. Mogelijk is het metabool syndroom één route die de link tussen depressie en hart- en vaatziekten kan verklaren. Het metabool syndroom bestaat uit een verzameling van risicofactoren voor hart- en vaatziekten zoals overgewicht (rondom de buik), hoge bloeddruk, verstoorde cholesterolwaardes, en verhoogde bloedsuikerspiegels. Er zijn aanwijzingen dat deze metabole verstoringen vaker voorkomen bij mensen met een depressie. Disfunctioneren van één van de meest belangrijke stress-systemen van het lichaam, de zogenaamde hypothalamus-hypofyse-bijnier (HPA)-as, zou een rol kunnen spelen in de relatie tussen depressie en het metabool syndroom. Bewijzen voor deze hypothesen komen voornamelijk voort uit dwarsdoorsnede onderzoek. In dit type onderzoek worden alle factoren, dus zowel depressie als metabole verstoringen, gemeten op hetzelfde moment waardoor men geen conclusies kan trekken betreffende oorzaak en gevolg. Ook is het zo dat eerdere onderzoeken de relatie tussen depressie en individuele metabole verstoringen vaak in afzondering van elkaar onderzocht hebben, terwijl ze juist vaak samen voorkomen zoals in het metabool syndroom. Met dit in het achterhoofd is het algemene doel van dit proefschrift te onderzoeken of depressieve symptomen vaak samen voorkomen met het metabool syndroom, of depressieve symptomen het ontstaan van metabole verstoringen voorspellen en, of depressieve klachten het gevolg zijn van metabole ontregelingen. Bovendien onderzoekt dit proefschrift of een verstoord functioneren van de HPA-as een rol speelt in de relatie tussen depressie aan de ene kant en het metabool syndroom en hart- en vaatziekten aan de andere kant. Kennis die met het onderzoek uit dit proefschrift verkregen wordt, vergroot ons begrip van de onderliggende biologische processen die depressie en hart- en vaatziekten met elkaar verbinden. Deze kennis zou gebruikt kunnen worden om preventie en behandeling van beide ziektes te verbeteren. Om deze vragen te kunnen beantwoorden worden gegevens gebruikt van enkele grote observationele studies. De nadruk ligt in dit proefschrift op ouderen, omdat depressieve symptomen en hart- en vaatziekten veel voorkomend zijn bij oudere mensen. Nadat een theoretische achtergrond geschetst wordt en het onderzoeksmodel gepresenteerd wordt in **Hoofdstuk 1**, zullen Hoofdstuk 2 tot en met 9 de onderzoeksresultaten rapporteren.

Als eerste wordt het verband tussen depressie en het metabool syndroom onderzocht met behulp van dwarsdoorsnede - oftewel cross-sectionele - gegevens. **Hoofdstuk 2** geeft verslag van gegevens van de Health, Aging and Body Composition (ABC) studie, een studie onder de algemene oudere Amerikaanse bevolking. In dit hoofdstuk wordt onderzocht of het metabool syndroom vaker vóórkomt bij mensen met psychosociale klachten (depressieve en angst symptomen, negatieve levensgebeurtenissen, en gebrek aan emotionele steun). In totaal doen 2917 blanke en zwarte mensen mee aan deze studie. Voor alle psychosociale factoren blijkt dat wanneer mensen hier last van hebben, ze ook vaker het metabool syndroom hebben. Wel wordt gevonden dat depressieve symptomen alleen een verband tonen met het metabool syndroom bij blanke mensen en angstsymptomen alleen bij mannen. Wanneer mensen tegelijkertijd meerdere psychosociale klachten hebben, is de samenhang met het metabool syndroom sterker. **Hoofdstuk 3** presenteert resultaten van de InCHIANTI studie onder 867 Italianen van 65 jaar en ouder. Ook in deze studie blijken mensen met depressieve symptomen vaker het metabool syndroom te hebben. Bevindingen van de Longitudinal Aging Study Amsterdam (LASA), onder 1212 deelnemers van 65 jaar en ouder, worden beschreven in **Hoofdstuk 4.** In tegenstelling tot de twee voorafgaande hoofdstukken, tonen de resultaten van deze studie niet aan dat mensen met een depressieve stoornis meer kans op het metabool syndroom hebben. Personen die last hebben van depressieve klachten zonder dat ze aan de criteria van een depressieve stoornis voldoen, hebben zelfs minder kans om het metabool syndroom te hebben.

Vervolgens is onderzocht of de HPA-as een rol speelt in de samenhang tussen depressie en het metabool syndroom. Cortisol spiegels, uit bijvoorbeeld urine of bloed, zijn een maat voor de activiteit van de HPA-as. In **Hoofdstuk 3**, gebaseerd op de InCHIANTI studie, blijkt dat de rol van cortisol erg belangrijk is. Het hierboven beschreven verband tussen depressieve symptomen en het metabool syndroom verdwijnt grotendeels nadat rekening wordt gehouden met cortisol spiegels in de urine. Deze resultaten duiden erop dat hoge cortisol spiegels een intermediaire rol spelen in de relatie tussen depressie en het metabool syndroom. Bovendien wordt gevonden dat alleen depressieve mensen met verhoogde cortisol spiegels een verhoogd risico op het metabool syndroom hebben. Bij depressieve personen blijken hoge cortisol spiegels vooral samen te hangen met een grote tailleomvang, hoge triglyceriden niveaus (hangen samen met het slechte cholesterol) en lage waardes van het high-density lipoprotein (HDL) cholesterol (het goede cholesterol). Hoewel in de LASA studie (**Hoofdstuk 4**) geen positieve relatie gevonden werd tussen depressie en het metabool syndroom, blijkt uit deze studie wel dat hoge cortisol spiegels samenhangen met het metabool syndroom. Dus ook uit deze studie kan men concluderen dat wanneer depressieve personen hoge cortisol waardes hebben, zij meer kans hebben op het metabool syndroom.

In een volgende stap wordt de temporele relatie tussen depressie en het metabool syndroom onderzocht, gebruikmakend van studies met meerdere meetmomenten over de jaren heen. Hierbij wordt speciale aandacht gegeven aan overgewicht (rondom de buik) omdat dit een centraal onderdeel is van het metabool syndroom. Uit onderzoek blijkt dat het

hebben van veel buikvet (met name het vet tussen de organen) grotere gezondheidsrisico's met zich meebrengt dan vet op andere plekken in het lichaam. **Hoofdstuk 5** onderzoekt of depressieve symptomen samenhangen met een toename in buikvet over 5 jaar. Gegevens van 2088 deelnemers aan het Health ABC onderzoek worden hiervoor gebruikt. Deze studie toont aan dat depressieve symptomen inderdaad gevolgd worden door een toename in buikvet, met name het vet tussen de organen. Deze toename in buikvet wordt niet veroorzaakt door een toename in algeheel overgewicht. Dit ondersteunt de gedachte dat de relatie tussen depressie en in het bijzonder buikvet deels verklaard kan worden door biologische mechanismen. Immers, wanneer psychologische of gedragsmatige mechanismen een belangrijke rol zouden spelen, zou ook een verband met algeheel overgewicht te verwachten zijn. In **Hoofdstuk 6** wordt, ook in de Health ABC studie, de tegenovergestelde richting onderzocht, namelijk of overgewicht (rondom de buik) het risico op het ontstaan van depressieve klachten verhoogd. Hiervoor worden 2547 personen onderzocht die op de beginmeting geen depressieve klachten hebben. Zowel algeheel overgewicht als overgewicht rondom de buik voorspellen het ontstaan van depressieve symptomen over 5 jaar bij mannen, maar niet bij vrouwen. Wanneer de effecten van algeheel overgewicht en buikvet tegelijkertijd bekeken worden, blijkt dat alleen het hebben van veel buikvet samenhangt met het ontstaan van depressieve klachten. Het verband tussen algeheel overgewicht en depressie lijkt dus te wijten aan het feit dat deze mensen ook veel buikvet hebben. Daarnaast blijkt dat buikvet vooral samenhangt met het ontstaan van depressieve symptomen die lang aanhouden. In **Hoofdstuk 7** wordt de vraag gesteld of het metabool syndroom samenhangt met het ontstaan en/of het blijven bestaan van depressieve symptomen. Gegevens van 823 deelnemers aan de InCHIANTI studie zijn hiervoor beschikbaar. Eerst wordt de groep mensen onderzocht die aanvankelijk vrij is van depressieve klachten. Uit de resultaten blijkt dat mensen met een grote tailleomvang meer kans hebben om depressieve symptomen te ontwikkelen. Voor geen enkel ander onderdeel van het metabool syndroom wordt deze relatie gevonden. Binnen de groep mensen mét depressieve klachten bij aanvang van de studie, blijkt het metabool syndroom gepaard te gaan met het blijven bestaan van de klachten. Dit geldt voor alle onderdelen van het metabool syndroom. De kans op een chronisch beloop van de depressieve klachten is drie maal groter wanneer een depressief persoon ook het metabool syndroom heeft. De bovenstaande bevindingen suggereren dat er een vicieuze cyclus bestaat tussen depressie en het opeenhopen van buikvet en de daarmee gepaard gaande metabole verstoringen. Deze vicieuze cyclus zou verantwoordelijk kunnen zijn voor het ontstaan van een chronisch subtype van depressie, welke gekarakteriseerd wordt door metabole verstoringen (een 'metabole depressie').

Tenslotte, om het onderzoeksmodel compleet te maken, worden in dit proefschrift enkele vooronderstelde verbanden met hart- en vaatziekten getest, te weten de relatie tussen HPA-as activiteit en hart- en vaatziekten en de relatie tussen depressie en hart- en vaatziekten. Onderzoek heeft aangetoond dat verschillende risicofactoren voor hart- en vaatziekten gepaard gaan met verhoogde activiteit van de HPA-as. Of hoge cortisol spiegels ook daadwerkelijk van invloed zijn op het optreden van ernstige hartproblemen is echter

nauwelijks onderzocht. In **Hoofdstuk 8** worden nogmaals de gegevens van 900 InCHIANTI deelnemers gebruikt. Ditmaal om te onderzoeken of cortisol waardes in urine een voorspellende waarde hebben ten aanzien van de totale sterfte en van sterfte door hart- en vaatziekten in het bijzonder, over een periode van 6 jaar. Uit de resultaten blijkt dat personen met hoge cortisol waardes in de urine een bijna 3 maal zo groot risico lopen om binnen 6 jaar aan een hart- en vaataandoening te overlijden. Het risico op overlijden in het algemeen is niet verhoogd. Deze bevindingen tonen aan dat hoge cortisol spiegels mogelijk specifiek schadelijk zijn voor het cardiovasculaire systeem. **Hoofdstuk 9** onderzoekt of het herhaaldelijk gevonden verband tussen depressie en hart- en vaatziekten ook zichtbaar is in een groep mensen met psychische klachten. Eerder onderzoek heeft zich bijna alleen maar gericht op de algemene bevolking en patiënten met hartklachten. Daarnaast wordt onderzocht wat de rol is van angststoornissen, die vaak gepaard gaan met een depressie. Voor deze vragen zijn gegevens beschikbaar van 2807 personen met een huidige depressie of angststoornis, een depressie of angststoornis in het verleden, en gezonde controle-personen die allen meedoen aan de Nederlandse Studie naar Depressie en Angst. Resultaten tonen aan dat personen met een huidige angststoornis bijna 3 maal zo vaak een aandoening aan de kransslagaders hebben in vergelijking met mentaal gezonde personen. Het meer vóórkomen van hartziekten onder depressieven lijkt voornamelijk te worden verklaard door het gegeven dat deze mensen daarnaast dikwijls een angststoornis hebben.

Dit proefschrift eindigt met een algemene discussie (**Hoofdstuk 10**) van de bevindingen in Hoofdstuk 2 tot en met 9. Samenvattend suggereert dit proefschrift dat het verband tussen depressie en het metabool syndroom in ouderen zich beperkt tot een subgroep van depressieve patiënten, namelijk diegenen met een verhoogde activiteit van de HPA-as. Over de tijd gezien, blijken depressieve symptomen en buikvet een twee-richtingen relatie te hebben. Wanneer beide aandoeningen aanwezig zijn, zorgen bijkomende metabole verstoringen er mogelijk voor dat de depressie meer chronisch verloopt. Deze resultaten ondersteunen het idee van een vicieuze cyclus en wijzen op het bestaan van een aparte aandoening die een metabole depressie genoemd zou kunnen worden. Alert zijn op metabole verstoringen bij depressieve patiënten zou hun lichamelijke gezondheidsstatus positief kunnen beïnvloeden en mogelijk zelfs hartaandoeningen kunnen voorkomen. Het moet nog onderzocht worden of behandeling van metabole verstoringen ook een gunstig effect heeft op het verbeteren van depressieve klachten.

Dankwoord

Het dankwoord. Het smeuïge stukje inside information dat als één van de eerste stukken gelezen wordt in je proefschrift (of ben alleen ik dat?) Wie gaat er bedankt worden? En wie niet? Hoe groot zijn de loftuitingen naar collega's, promotoren en partner? Natuurlijk ben ik ook een aantal mensen dank verschuldigd voor hun directe of indirecte steun of bijdrage aan mijn proefschrift. Dus hier komen ze!

Uiteraard begin ik met mijn promotoren te bedanken.
Beste Brenda, ik heb veel van jou geleerd. Hoe zeggen ze dat ook al weer: "goed voorbeeld, doet goed volgen"? Dankjewel voor je vele én snelle input op alle stukken die ik je in de afgelopen jaren heb voorgelegd. Voor het overzicht dat jij steeds behield en voor het feit dat ik altijd wel even bij je aan kon kloppen, hoe druk je het ook hebt. Ik hoop dat we ook na mijn promotie nog een tijd fijn samen zullen werken.
Beste Aartjan, iets meer op een afstandje was jij goed in staat advies te geven over wat bijvoorbeeld een artikel nog nodig had. "Wat is nu precies de klinische relevantie van wat je onderzocht hebt?", "Je moet de lezer bij de hand nemen en hen elk stapje uitleggen". Wanneer je zelf met je neus diep in de data zit is het fijn iemand te hebben die je daaruit trekt en vraagt wat je nou eigenlijk aan het doen bent! Dank daarvoor!

In addition I would like to thank *all my co-authors* for their valuable input into the papers that are the result of my PhD project. In particular, I would like to thank the key persons who allowed me to make use of their extensive datasets from large scaled cohort studies, *Stephen Kritchevsky* (Health ABC), *Luigi Ferrucci* (InCHIANTI study) and *Dorly Deeg* (LASA). Thanks for the fruitful collaborations! Dank voor de samenwerking! *Dear Steve*, I also appreciate I was welcome to visit the Sticht Center on Aging, in Winston-Salem, North Carolina. For several months I had the chance to work in a different setting and country. I really got inspired by gerontological research during that period! *Dear Denise*, although we never made it to co-authors, I'd like to thank you for you looking after me and being a very pleasant colleague during my time in W-S. Ook wil ik de stagiaires, Lisette, Gerard, Manon en Ingrid niet vergeten die in meer of mindere mate hebben bijgedragen aan de inhoud van dit proefschrift. Verder wil ik hier graag de leden van mijn beoordelingcommissie bedanken omdat zij bereid zijn mij op 23 april grondig aan de tand te voelen.

Dan, niet te vergeten: mijn directe collega's. De mensen waarmee je dagelijks je bezigheden als AIO deelt en die je promotietraject van dichtbij meemaken. *Beste Sophie*, dankjewel voor al die keren dat je tijd voor me maakte als ik bij je aanklopte om je een probleem voor te leggen of een vraag had over cortisol, of gewoon om even een praatje te maken. Ik vind het heel leuk dat je mijn paranimf wilt zijn! Ook mijn andere mede-AIO's, Carmilla, Didi, Inger, Jenneke en Adrie wil ik bedanken voor hun hulp, luisterend oor en vooral gezelligheid. *Beste Carmilla*, ik hoop dat we nog een tijdje collega's blijven en in de toekomst meer gaan samenwerken. *Beste Didi*, in het begin van mijn AIO-schap hebben we eventjes een kamer gedeeld. Dat was een leuke tijd, jammer dat je onderzoekstijd nu heel spaarzaam is. *Beste Inger*, je hebt als één van de eersten het NESDA-nest verlaten, maar we houden contact! *Beste Jenneke,* hopelijk blijven we je nog wel met regelmaat zien als je

zo meteen in opleiding bent. *Beste Adrie*, het was gezellig samen in Chicago, hopelijk volgen er nog meer gezamenlijke congressen! Beste allemaal, ook al is onze intervisie nooit echt van de grond gekomen, de avondjes dat we bij elkaar gegeten hebben, waren erg gezellig! Net zoals de (iets te weinig) gezamenlijke buiten-de-deur-lunches en borrels! Hopelijk kunnen we deze losvaste traditie voortzetten nu iedereen langzaamaan zijn eigen richting opgaat. Ook alle andere collega's bij NESDA/psychiatrie, in het bijzonder *Femke, Marissa, Carla, Suzie, Tim en Reen*: bedankt voor de fijne werkomgeving. *Lynn en Josine*, dankjewel voor het plezier dat ik heb in het begeleiden van jullie!

Natuurlijk zijn er ook een aantal mensen buiten werk die ik wil bedanken. *Lieve Dagmar*, we zijn al 12½ jaar goede vriendinnen. Ook al zien we elkaar de laatste jaren wat minder dan tijdens onze studententijd, ik waardeer onze vriendschap enorm en hoop dat we nog lang vriendinnen zullen blijven. Ik ben heel blij dat jij tijdens mijn promotie naast me staat als paranimf! *Lieve Femke,* wij kennen elkaar zelfs nog langer! Onze 'afspraakjes' zijn altijd heel gezellig en dat moeten we zeker blijven volhouden. Dankjewel dat je een lieve vriendin voor me bent. *Lieve mam en pap*, bedankt voor jullie goede zorgen en voor het creëren van een fijn thuis. Jullie zijn echte doorzetters, wat er ook gebeurt. Dankjewel voor het bijbrengen van zo'n goede eigenschap! *Lieve Alain en Maurice*, het is fijn om twee grote broers als jullie te hebben. *Lieve Chantal*, mijn allerliefste grote zus, jij hebt me geïnspireerd voor de wetenschap (en zoveel meer). Jij hebt jouw promotie helaas nooit af kunnen maken, maar ik hoop dat je nu trots op me zou zijn geweest. Ik mis je. Tot slot, *lieve Richard*, waar moet ik beginnen? Dankjewel dat je er voor mij bent!

x Nicole

Curriculum Vitae

Nicole Vogelzangs werd op 14 oktober 1978 geboren in het Noord-Limburgse dorpje Lomm, gemeente Arcen en Velden. Zij behaalde haar gymnasium diploma in 1997 aan het Thomas College in Venlo. Hierna volgde ze de opleiding Biologische Psychologie met een specialisatie in Neuropsychologie aan de Universiteit van Maastricht. Tijdens haar studie verbleef zij zes maanden in Montreal, Canada. Hier deed ze een onderzoeksstage aan the Department of Psychiatry, McGill University naar de effecten van zuurstof op de aanmaak van serotonine. In 2005 begon zij als promovenda bij GGZ inGeest, afdeling Psychiatrie en EMGO$^+$ van het VU medisch centrum, Amsterdam. Zij onderzocht de relatie tussen depressie en het metabool syndroom met dit proefschrift als eindresultaat. Als onderdeel van haar promotieonderzoek dat grotendeels gebaseerd is op Amerikaanse data, bezocht zij in 2006 voor vier maanden het Sticht Center on Aging, aan het Wake Forest University Baptist Medical Center in Winston-Salem, North Carolina in de Verenigde Staten. Daarnaast volgde ze de postinitiële opleiding epidemiologie verzorgd door EMGO$^+$ in Amsterdam en behaalde deze master in 2007. Vanaf juli 2008 hebben haar onderzoeksactiviteiten zich uitgebreid buiten haar promotieonderzoek. In januari 2010 begon Nicole aan een 2-jarig fellowship beschikbaar gesteld door EMGO$^+$ om, voortbordurend op haar proefschrift, de rol van ontstekingsfactoren in depressie en angst en in hun relatie met somatische aandoeningen te onderzoeken. Nicole woont in Maarssen samen met haar partner Richard Gubbels en kat Pippa.

Nicole Vogelzangs was born on October 14, 1978 in Lomm a little village in the North of Limburg, the Netherlands. She graduated from high school (gymnasium) in 1997 at the Thomas College in Venlo. After this she studied Biological Psychology with a specialization in Neuropsychology at the Maastricht University. During her study she spent six months in Montreal, Canada. Here she did a scientific internship at the Department of Psychiatry, McGill University on the effects of oxygen on serotonin synthesis. In 2005 she started as PhD student at GGZ inGeest, department of Psychiatry and EMGO$^+$ at the VU University Medical Center, Amsterdam. She investigated the association between depression and metabolic syndrome, which resulted in this thesis. As part of her PhD project, largely based on American data, she visited the Sticht Center on Aging at the Wake Forest University Baptist Medical Center in Winston-Salem, North Carolina in de United States in 2006 for four months. In addition, she obtained a masters degree in epidemiology in 2007. Since July 2008 her research activities have elaborated beyond her PhD project. In January 2010 Nicole started a 2-year fellowship funded by EMGO$^+$ to follow up on her PhD research, examining the role of inflammatory markers in depression and anxiety and in their relationship with somatic diseases. Nicole lives in Maarssen together with her partner Richard Gubbels and Pippa the cat.

List of Publications

First author publications

Vogelzangs N, Seldenrijk A, Beekman AT, van Hout HP, de Jonge P, Penninx BW. Cardiovascular disease in persons with depressive and anxiety disorders. Journal of Affective Disorders 2010; in press.

Vogelzangs N, Kritchevsky SB, Beekman AT, Brenes GA, Newman AB, Satterfield S, Yaffe K, Harris TB, Penninx BW. Obesity and onset of significant depressive symptoms: results from a prospective community-based cohort study of older men and women. Journal of Clinical Psychiatry 2009; Dec 15. Epub ahead of print.

Vogelzangs N, Beekman AT, Dik MG, Bremmer MA, Comijs HC, Hoogendijk WJ, Deeg DJ, Penninx BW. Late-life depression, cortisol and the metabolic syndrome. American Journal of Geriatric Psychiatry 2009; 17(8): 716-721.

Vogelzangs N, Kritchevsky SB, Beekman AT, Newman AB, Satterfield S, Simonsick EM, Yaffe K, Harris TB, Penninx BW. Depressive symptoms and change in abdominal obesity in older persons. Archives of General Psychiatry 2008; 65(12): 1386-1393.

Vogelzangs N, Penninx BW. Cortisol and insulin in depression and metabolic syndrome. Letter to the editor. Psychoneuroendocrinology 2007; 32(7): 856.

Vogelzangs N, Beekman AT, Kritchevsky SB, Newman AB, Pahor M, Yaffe K, Rubin SM, Harris TB, Satterfield S, Simonsick EM, Penninx BW. Psychosocial risk factors and the metabolic syndrome in elderly persons: findings from the Health, Aging, and Body Composition study. Journal of Gerontology: Medical Sciences 2007; 62(5): 563-569.

Vogelzangs N, Suthers K, Ferrucci L, Simonsick EM, Ble A, Schrager M, Bandinelli S, Lauretani F, Giannelli SV, Penninx BW. Hypercortisolemic depression is associated with the metabolic syndrome in late-life. Psychoneuroendocrinology 2007; 32(2): 151-159.

Submitted

Vogelzangs N, Beekman AT, Milaneschi Y, Bandinelli S, Ferrucci L, Penninx BW. Urinary cortisol and 6-year risk of all-cause and cardiovascular mortality.

Vogelzangs N, Beekman AT, Boelhouwer IG, Bandinelli S, Milaneschi Y, Ferrucci L, Penninx BW. Metabolic depression: a chronic depressive subtype.

Co-author publications

Penninx BW, **Vogelzangs N**. Aging and behavioral medicine. In: Steptoe A et al. Handbook of Behavioral Medicine. Springer. In press.

Licht CM*, Vreeburg SA*, van Reedt-Dortland AK, Giltay EJ, Hoogendijk WJ, de Rijk RH, **Vogelzangs N**, Zitman FG, de Geus EJ, Penninx BW. Increased sympathetic and decreased parasympathetic activity rather than changes in hypothalamic-pituitary-adrenal-axis activity are associated with metabolic abnormalities. Journal of Clinical Endocrinology & Metabolism 2010; in press. * Joint first authors.

Klabbers G, Bosma H, van der Does AJ, **Vogelzangs N**, Kempen GI, van Eijk JT, Penninx BW. The educational pattering of health-related adversities in individuals with major depression. Journal of Affective Disorders 2010; in press.

Seldenrijk A, **Vogelzangs N**, van Hout HP, van Marwijk HW, Diamant M, Penninx BW. Depressive and anxiety disorders and risk of subclinical atherosclerosis: findings from the Netherlands Study of Depression and Anxiety (NESDA). Journal of Psychosomatic Research 2010; in press

Van Mill JG, Hoogendijk WJ, **Vogelzangs N**, van Dyck R, Penninx BW. Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders. Journal of Clinical Psychiatry 2010; 71(3):239–246.

Furberg H, Fortmann SP, Absher D, Quertermous T, Assimes TL, Knowles JW, Iribarren C, Kim Y, Franceschini N, Boerwinkle E, Kraft P, Gu F, Hunter DJ, Hankinson SE, Chanock S, Lips EH, McKay JD, Zaridze D, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, Benhamou S, Lagiou P, Holcátová I, Richiardi L, Kjaerheim K, Agudo A, Castellsagué X, Macfarlane TV, Barzan L, Canova C, Lowry R, Conway DI, Znaor A, Healy C, Lanthrop M, Brennan P, Penninx BW, Smit JH, **Vogelzangs N**, Vink JM, Boomsma DI, Willemsen G, de Geus EJ, Jackson AU, Mohlke KL, Stringham HM, Boehnke M, Tuomilehto J, Ardissino D, Bernardinelli L, Mannucci PM, Mauri F, Merlini PA, Preis SR, Hwang SJ, Ramachandran VS, Benjamin EJ, Levy D, Everett B, Pare G, Chasman D, Ridker P, Groop L, Almgren P, Ladenvall C, Sanders AR, Levinson DF, Duan J, Shi J, Gejman PV, Perry J, Guralnik J, Bandinelli S, Milaneschi Y, Frayling T, Tanaka T, Ferrucci L, Psaty B, Thacker E, Bis J, McKnight B, Furberg C, Haritunians T, Taylor K, Lucas G, Elosua R, Schwartz SM, Salomaa V, Voight BF, Melander O, O'Donnell CJ, Tiemeier H, Hofman A, van Duijn CM, Walter S, Uitterlinden AG, Lin DY, Kraft P, Ioannidis JP, Posthuma D, Lerman C, Kaprio J, Maes H, Thornton L, McGovern JA, Rose J, Li MD, Dackor J, Sullivan P. Meta-analyses of genome wide association studies implicate multiple loci for smoking behavior. Nature Genetics 2010; in press.

Lind PA, Macgregor S, Vink JM, Pergadia ML, Hansell NK, de Moor MH, Smit AB, Hottenga JJ, Richter MM, Heath AC, Martin NG, Willemsen G, de Geus EJ, **Vogelzangs N**, Penninx BW, Whitfield JB, Montgomery GW, Boomsma DI, Madden PA. A genomewide association study of nicotine and alcohol dependence in Australian and Dutch populations. Twin Research and Human Genetics 2010; 13(1): 10-29.

Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Mägi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JRB, Egan JM, Lajunen T, Grarup N, Sparsø T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proença C, Kumari M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccasecca RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben-Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Böttcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen Y, Chines P, Clarke R, Coin LJM, Cooper MN, Cornelis M, Crawford G, Crisponi L, Day INM, de Geus E, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R, Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllensten U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen A, Hassanali N, Hayward C, Heath SC, Hercberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PRV, Jørgensen T, Jula A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Bacquer OL, Lecoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martínez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orrù M, Pakyz R, Palmer CNA, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AFH, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurðsson G, Sijbrands EJG, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvänen A, Tanaka T, Thorand B, Tichet J, Tönjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varma D, Visvikis-Siest S, Vitart V, **Vogelzangs N**, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemsen G, Witteman JCM, Yarnell JWG, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, DIAGRAM Consortium, GIANT Consortium, Global BPGen Consortium, Borecki IB, Loos RJF, Meneton P, Magnusson PKE, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Ríos M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WHL, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP, Wichmann HE, Illig T, Rudan I, Wright AF, Stumvoll M, Campbell H, Wilson JF, Hamsten A on behalf of Procardis consortium, Bergman RN, Buchanan TA, Collins FS, Mohlke KL, Tuomilehto J, Valle TT, Altshuler D, Rotter JI, Siscovick

DS, Penninx BWJH, Boomsma D, Deloukas P, Spector TD, Frayling TM, Ferrucci L, Kong A, Thorsteinsdottir U, Stefansson K, van Duijn CM, Aulchenko YS, Cao A, Scuteri A, Schlessinger D, Uda M, Ruokonen A, Jarvelin M, Waterworth DM, Vollenweider P, Peltonen L, Mooser V, Abecasis GR, Wareham NJ, Sladek R, Froguel P, Watanabe RM, Meigs JB, Groop L, Boehnke M, McCarthy MI, Florez JC and Barroso I. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nature Genetics 2010; 42(2): 105-116.

Estrada K, Krawczak M, Schreiber S, van Duijn K, Stolk L, van Meurs JB, Liu F, Penninx BW, Smit JH, **Vogelzangs N**, Hottenga JJ, Willemsen G, de Geus EJ, Lorentzon M, von Eller-Eberstein H, Lips P, van Schoor N, Pop V, de Keijzer J, Hofman A, Aulchenko YS, Oostra BA, Ohlsson C, Boomsma DI, Uitterlinden AG, van Duijn CM, Rivadeneira F, Kayser M. A genome-wide association study of northwestern Europeans involves the C-type natriuretic peptide signaling pathway in the etiology of human height variation. Human Molecular Genetics 2009; 18(18): 3516-3524.

Morsink LF, **Vogelzangs N**, Nicklas BJ, Beekman AT, Satterfield S, Rubin SM, Yaffe K, Simonsick EM, Newman AB, Kritchevsky SB, Penninx BW. Associations between sex steroid hormone levels and depressive symptoms in elderly men and women: results from the Health ABC study. Psychoneuroendocrinology 2007; 32(8): 874-883.

Nishikawa M, Kumakura Y, Young SN, Fiset P, **Vogelzangs N**, Leyton M, Benkelfat C, Diksic M. Increasing blood oxygen increases an index of 5-HT synthesis in human brain as measured using alpha-[^{11}C]methyl-L-tryptophan and positron emission tomography. Neurochemistry International 2005; 47(8): 556-564.

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